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THE PATHOLOGY OF "ICTERUS CATARRHALIS" *

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A satisfactory definition of the term "catarrhal jaundice" can hardly be given, since it is more than doubtful that this term actually designates only one clinical entity of the same etiology and pathogenesis. The use of the term is today more a matter of convenience than an expression of the belief that a catarrhal condition of the common duct has been the cause of an obstruction of the outflowing bile. Eppinger [1] quite rightly maintains that "every case of jaundice with a sudden onset, lasting one to several weeks, giving a favorable prognosis should be included in the group of icterus catarrhalis provided the diagnosis cholelithiasis can be ruled out."

The idea that jaundice frequently depends on gastroduodenitis was first expressed by F. J. V. Broussais.[2] Stokes,[3] in his lectures, gives an exact description of a condition which at present would belong in the group of catarrhal jaundice. He lays great emphasis on the relationship which exists between "inflammation of the upper digestive tube" and jaundice. It must be mentioned that Stokes believed that the icterus was "independent of any mechanical obstruction of the gall bladder or biliary ducts." He thought that the liver "sympathetically partakes in the irritation of the stomach and duodenum and that as a consequence of this the biliary secretion is arrested." It must not be overlooked, however, that Stokes, although fully familiar with the picture of the

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1. Eppinger, in Kraus and Brugsch: Specielle Pathologie und Therapie innerer Krankheiten, Urban and Schwarzenberg **6**:2, 1923.

2. Broussais, F. J. V.: Principles of Physiological Medicine, Philadelphia, Carey and Lea, 1923.

3. Stokes: London M. & S. J. **5**:198, 1839.

benign jaundice, today commonly called catarrhal jaundice, included in his conception of gastroduodenal icterus clinical entities of a very serious nature. For instance, it seems to him "that the yellow fever of warmer climates is only a variety of jaundice depending upon irritation of the gastro-intestinal surface." The insufficient description of his post-mortem observations does not permit a diagnosis of the other cases which Stokes included within the group of gastroduodenal jaundice. According to his ideas, however, the icterus, depending on gastroduodenitis, frequently could be fatal. In that respect Stokes' ideas of gastroduodenal icterus do not conform with our present conception of its benign nature. Graves [4] makes short mention of gastroduodenitis among the various causes of jaundice. The teaching of the great English clinicians was soon generally accepted. Bamberger,[5] Frerichs,[6] and Leyden [7] describe gastroduodenal jaundice as an important and frequent disease of the liver. Contrary, however, to Stokes' explanation, they maintain that the jaundice following gastroduodenitis is caused by a catarrhal swelling of the ostium of the common duct. The disease is, according to the German authors, benign and the occasion for anatomic observation is rare (Bamberger). It seems surprising to note how generally accepted was the belief that catarrhal jaundice was caused by an extension of the preceding duodenitis into the ostium of the common duct in spite of the lack of anatomic observation, far more so since scientific medicine at that period was entirely dependent on the observations of pathologic anatomy. The conception, however, was greatly supported by Virchow's [8] famous statements about the anatomic observations in catarrhal jaundice, namely: (1) swelling of the ostium of the common duct, (2) obstruction of its lumen by a whitish plug composed of epithelial masses and (3) sudden dilatation of the bile-stained common duct above its intestinal portion. The authoritative support and the plausibility of the explanation make it clear that the mechanism of this type of jaundice was generally accepted to be that of obstructive icterus. A critical review of Virchow's article, however, makes it rather doubtful whether his observations actually refer to cases of catarrhal jaundice in our modern conception. The case which occasioned his earliest considerations [9] on catarrhal jaundice was an icterus of unknown origin in a

4. Graves: Clinical Lectures on the Practice of Medicine, Dublin, Famin & Co., 1864, p. 632.

5. Bamberger: Krankheiten des chylopoetischen Systems, in Virchow: Handbuch der Pathologie und Therapie, Erlangen, Ferdinand Enke, **6,** 1855.

6. Frerichs: Clinic der Leberkrankheiten, Braunschweig, Friederich Vierweg und Sohn, 1858.

7. Leyden: Beiträge zur Pathologie des Ikterus, Berlin, August Hirschwald, 1866, p. 102.

8. Virchow: Virchows Arch. f. path. Anat. **32:**117, 1864.

9. Virchow: Wien. med. Wchnschr. **8:**409, 1858.

puerpera and certainly did not belong in the group of gastroduodenal jaundice. His second paper, however, deals with catarrhal jaundice in general without case reports.

The theory of the obstructive nature of the catarrhal jaundice was first challenged by Heitler,[10] who considered it a generalized disease with parenchymatous degeneration of the liver. Also Pal [11] "believed that the majority of cases of catarrhal jaundice were due to an infectious generalized disease not the result of a catarrhal affection of the duodenum."

Whereas such contradictions of the generally accepted teachings were only sporadic we find at the beginning of the twentieth century a greater number of authors attacking the old conception from various sides. The doubt of the correctness of the old conception is well expressed in the introductory words of Quincke.[12] "From the differences seen in the various clinical pictures of catarrhal jaundice and from the uncertainty of the anatomical findings we are forced to the conclusion that this disease is not a clinical entity but is composed of a group of different conditions varying with the anatomic seat of the trouble and the mode of origin." Clinical observations, as for instance the occurrence of fever, hepatic and splenic enlargement with tenderness, the frequently prolonged course of the disease after the initial gastro-intestinal symptoms have long subsided contradicted the conception of a simple catarrhal swelling of the porus biliaris as the only cause of acute catarrhal jaundice. It suggested extension of the inflammatory process into the upper part of the common duct and its larger branches and even an inflammation of the finer bile ducts, an angiocholitis (Gerhard,[13] Pel,[14] Ewald [15]). Naunyn,[16] however, strictly upholds the old conception and separates cholangitis from catarrhal jaundice. Strisower,[17] in a recent paper, believes that there is extension of the duodenitis into the large biliary ducts in catarrhal icterus, but he thinks that cholangitis can be separated clinically and by laboratory means, although it may start like catarrhal jaundice. His cases diagnosed as cholangitis did not show initial gastro-intestinal disturbances and showed a rather severe course. Contrary to the cases he considered as acute catarrhal jaundice, cholangitis shows only partial biliary obstruction and albuminocholia. His icterus catarrhalis conforms with Type I of Eppinger's classification of the whole

10. Heitler, M.: Wien. med. Wchnschr. **37**:957, 1887.
11. Pal, J.: Wien. klin. Wchnschr. **7**:19, 1894.
12. Quincke: Nothnagel's Encyclopedia, New York, W. B. Saunders Company, 1903.
13. Gerhard: München. med. Wchnschr. **52**:889, 1905.
14. Pel: Die Krankheiten der Leber, Jena, G. Fischer, 1909.
15. Ewald: Die Leberkrankheiten, Leipzig, Georg Thieme, 1913.
16. Naunyn: Mitt. a. d. Grenzgeb. d. Med. u. Chir. **31**:537, 1918-1919.
17. Strisower: Wien. Arch. f. inn. Med. **3**:153, 1922.

group and nearly with the icterus simplex duodenalis of Felsenreich and Satke.[18] Although his differential diagnostic considerations appear sound, it is not conclusive that his cases considered as cholangitis are actually caused by inflammation of the small bile ducts, and it is questionable whether a differentiation from his catarrhal jaundice is always possible. In our review, Mayo-Robson's [19] theory must not be forgotten, who believes that acute catarrhal jaundice is caused by a pancreatitis, the result of extension of an inflammation from the duodenum to the pancreatic duct (Deaver [20]). Although the theories propounded by most of the authors mentioned above differ considerably from Virchow's conception, the obstructive mechanism of catarrhal jaundice and its relationship to gastroduodenitis remains unchallenged.

A critical observer, however, could not fail to notice that a great number of cases of icterus which conformed in many respects with the familiar clinical picture of catarrhal jaundice did not show initial gastrointestinal symptoms (about half of the seventy cases of pure noncomplicated icterus in Ewald's [15] observations). On the other hand, icterus seems relatively rare compared with the great frequency of acute gastroduodenitis (Pel [14]). Bamberger [5] has already called attention to the relationship existing between colds and jaundice (icterus vernalis). Jones and Minot [21] and Blumer [22] also lay stress on icterus starting with upper respiratory disease. From these facts the conclusion had to be drawn that a considerable number of cases of simple jaundice were not dependent on gastroduodenitis. Nevertheless, the term "catarrhal jaundice" was not abandoned because of the close resemblance in the clinical picture with those cases which were preceded by gastroduodenitis.

The occasional outbreak of icterus among larger or smaller groups of patients has suggested an infectious origin and, such cases have been commonly designated as infectious jaundice.[23] The clinical picture of the afebrile epidemic cases did not differ from that of the common catarrhal jaundice (Blumer [22]). Therefore several authors plead for an identification of sporadic catarrhal and epidemic infectious icterus—

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18. Felsenreich and Satke: Arch. f. Verdaunngskr. **32**:21, 1924

19. Mayo-Robson, in Albutt and Rolleston: A System of Medicine, London, Macmillan & Co., Lt. **2**:1, 1908.

20. Deaver: Ann. Surg. **81**:287, 1925.

21. Jones, C., and Minot, G.: Boston M. & S. J. **189**:531, 1923..

22. Blumer, G.: Infectious Jaundice in the United States, J. A. M. A. **81**:353 (Aug. 4) 1923.

23. The fact has been neglected that the term had already been in use in the German literature for the morbid entity described by Weil (Deutsches Arch. f. klin. Med. **39**:209, 1886), with an entirely different clinical picture. That oversight is of no importance any more since the etiologic term has replaced the old designation (Tuada, Ido, Hoki, Kaneko and Ho, J. Exper. Med. **23**:377, 1916).

Costa and Troisier,[24] Brugsch and Schürer,[25] Jones and Minot.[21] Brulé [26] believes that "the benign infectious jaundice is only a more serious variety of the catarrhal icterus."

It is not surprising that the supposed infectious origin of jaundice stimulated bacteriologic research. Widal, Lemierre and Bernard [27] were the first to report a case of benign icterus in the course of a septicemia due to a paracolon bacillus. Sarrailhe and Clunet [28] describe the frequent occurrence of an atypic *bacillus paratyphosus* in the blood of patients during an epidemic of icterus of very benign nature. Clinically manifestations of cholecystitis were frequent. Similar observations were made by Carnot and Weile-Halle [29] in a family suffering with a mild form of icterus. The report of Cantacuzene [30] deserves to be mentioned. He observed an extensive epidemic in the Roumanian army caused by *B. paratyphosus*. The course of the icterus was very benign, among thousands of cases only four being fatal. Necropsy revealed a severe angiocholitis of the intralobular canaliculi. According to Cantacuzene, it was impossible to determine whether the infection was hematogenous or ascending. Anigstein and Milinska [31] examined ninety-three cases of jaundice, sixty-seven of which were diagnosed as icterus catarrhalis. Agglutination tests were made with seventeen different strains of the paratyphoid group. Eighty per cent of the cases agglutinated the strain Aertrycke-Stanley. Lippmann [32] saw several cases of icterus due to *B. paratyphosus* and typhosus. Olivet [33] found *B. coli* in the liver puncture in a case of catarrhal jaundice. Contrary to these positive observations, Brugsch and Schürer [25] found bacilli of the colon-typhoid group in only a very small percentage of their cases. In his review of the American icterus epidemics of the years 1920-1922, Blumer [22] emphasizes that no definite bacterial cause was found in the United States.

We are greatly indebted to the school of Chauffard and Widal for the inauguration of systematic bacteriologic research in jaundice. The question of the etiology might still be controversial, but as a result of their work the hematogenous infectious origin of a great many cases of epidemic and sporadic jaundice can no more be questioned. Clinical observations point to inflammatory lesions of the smaller and larger bile

24. Costa, S., and Troisier, J.: Ann. de med. **16**:180, 1924.
25. Brugsch, T., and Shürer, J.: Deutsche med. Wchnschr. **56**:601, 1919.
26. Brulé: Recherches sur les ictéres, ed. 3, Paris, Masson et Cie, 1922.
27. Bernard, R.: Soc. méd. d. hôp. de Paris **28**:776, 1909.
28. Sarrailhe, A., and Clunet, J.: Soc. méd. d. hôp. de Paris **40**:45, 1916.
29. Carnot, P., and Weile-Halle, B.: Soc. méd. d. hôp. de Paris **39**:377, 1915.
30. Cantacuzene, J.: Presse méd. **26**:541, 1918.
31. Anigstein, L., and Milinska, Z.: Centralbl. f. Bakteriol. **91**:383, 1923-1924.
32. Lippmann, A.: Med. Klin. **18**:1176, 1922.
33. Olivet, J.: Klin. Wchnschr. **5**:307, 1926.

passages, and few anatomic and experimental observations (Fränkel,[34] Cantacuzene [30]) seem to confirm the belief that the infectious benign jaundice is due to acute hematogenous cholangeitis. Fränkel concludes from his observation that "even in cases of so-called icterus catarrhalis a hematogenous infection of the biliary passages has to be considered." Lippmann [32] and Umber [35] express the same opinion.

However, the majority of recent writers do not agree with a generalization of that conception. For instance, Brulé questions whether the angiocholitis found in infectious jaundice is really primary, and points out that cholangeitis is by no means always accompanied by icterus. Stokes,[3] as mentioned above, did not believe in the obstructive nature of gastroduodenal jaundice, and attributed the icterus to a concommitant (sympathetic) alteration of the liver. Doubtless his conception lacks precision, but it is interesting to see that the great physician already recognized the rôle of the liver parenchyma in catarrhal jaundice. Clinical observation had led Heitler [10] and Pal [11] to the belief that this form of icterus was not as harmless as generally accepted. With a mere catarrhal swelling of the porus biliaris, the frequent prolonged course and the rather serious subsequent constitutional symptoms, as anemia, loss of weight, extreme weakness, etc., could hardly be explained. Chauffard [36] was the first to point to the insufficiency of the liver in catarrhal jaundice because of his observations of alimentary glycosuria and intermittent elimination of methylene blue. Minkowski [37] "refrains from the use of the designation 'catarrhal,' because in its conception a definite mode of development of the jaundice has been assumed and this has by no means been proven in all cases." He believes in special functional disturbances of the hepatic cells as the cause of the so-called catarrhal jaundice. With the development of numerous laboratory tests, there was an opportunity to examine the various functions of the liver in catarrhal jaundice. Bauer's galactose test gave strongly positive results according to Bondi and König,[38] Bauer,[39] and Reid and Jehn.[40] Alterations in the nitrogenous metabolism, as to be expected in liver injury (Chesney, Marshall and Rowntree [41]), have been reported by

34. Fränkel, E.: München. med. Wchnschr. **65**:523, 1918.

35. Umber, F.: Klin. Wchnschr. **3**:573, 1923.

36. Chauffard, in Bouchard and Brissaud: Traité de médecine, ed. 2, Paris, Masson et Cie, **5**, 1902.

37. Minkowski, in Billings: Diseases of the Digestive System, New York, D. Appleton & Co., 1906, p. 325.

38. Bondi, S., and König, F.: Wien. med. Wchnschr. **60**:2617, 1910.

39. Bauer, R.: Sémaine méd. **76**:288, 1912.

40. Reid, E., and Jehn, W.: Deutsches Arch. f. klin. Med. **108**:187, 1912.

41. Chesney, A. M.; Marshall, E. K., Jr., and Rowntree, L. G.: Studies in Liver Function, J. A. M. A. **63**:1533 (Oct. 31) 1914.

Oddo.[42] Decrease in the blood fibrinogen has been found by Adler.[43] The phenoltetrachlorphthalein test indicated an insufficiency of the liver (Rosenthal,[44] Ottenberg, Rosenfeld and Goldsmith[45]). Hatieganu[46] reports lack of excretion of indigo-carmine in catarrhal jaundice; Widal, Abrami and Jancovesco,[47] positive hemoclasic crisis in three cases. In a comparative study of the recent tests for liver function, Shattuck, Browne and Preston[48] found impaired liver function in five cases of catarrhal jaundice. The occurrence of dissociated icterus suggests an alteration of the liver cell, according to Brulé.[26]

From such experiences the conclusion has been drawn that alterations of the liver parenchyma are responsible for a great number of cases of so-called catarrhal jaundice. Such a point of view is expressed in numerous articles of the world literature—Jones,[49] Minot,[21] Brulé[26] Oddo,[42] Eppinger, Lepehne,[50] Retzlaff,[51] Ruge[52] and Bauer.[53] It is rather surprising, however, to see that most of our modern English encyclopedias, as Tice's "Practice of Medicine," "Oxford Medicine," Nelson's "Loose-Leaf Living Medicine," have not yet taken notice of the changes in the theory of the pathogenesis of catarrhal jaundice and still give in brief the old mechanistic explanation. An exception was found in the tenth edition of Osler and McCrae's "Principles and Practice of Medicine" and in the "Compendium of Pathology," edited by Dr. G. T. Bell for the students of the University of Minnesota. The reports dealing with catarrhal jaundice from the clinical and functional aspects are as numerous as the morphologic observations on record are scarce.

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42. Oddo, J.: Gaz. d. hôp. **93**:1501, 1920.

43. Adler, A.: Klin. Wchnschr. **3**:978, 1924.

44. Rosenthal, S. M.: Phenoltetrachlorphthalein Test for Hepatic Function, J. A. M. A. **83**:1049 (Oct. 4) 1924.

45. Ottenberg, R.; Rosenfeld, S., and Goldsmith, L.: Clinical Value of Serum-Tetrachlorphenolphthalein Test for Liver Function, Arch. Int. Med. **34**:206 (Aug.) 1924.

46. Hatieganu, J.: Ann. de méd. **10**:400, 1921.

47. Widal, F.; Abrami, P., and Jancovesco, N.: Compt. rend. Acad. d. Sc. **171**:148, 1920.

48. Shattuck, H. F.; Browne, J. C., and Preston, M.: Am. J. M. Sc. **170**:510, 1925.

49. Jones, C. M.: Blood Pigment Metabolism and Its Relation to Liver Function, Arch. Int. Med. **29**:643 (May) 1922.

50. Lepehne: Ergebn. d. inn. Med. und Kinderh. **20**:221, 1921.

51. Retzlaff, K.: Ztschr. f. die ges. exper. Med. **34**:1933, 1923; Deutsche med. Wchnschr. **47**:798, 1921.

52. Ruge, H.: Klin. Wchnschr. **4**:1166, 1925.

53. Bauer, R.: Wien. Arch. f. inn. Med. **6**:9, 1923.

REPORT OF CASES

CASE 1 (Neusser and Tölg[54]).—A man, aged 39, with a history characteristic of catarrhal jaundice, during his stay in the hospital developed severe symptoms of hemorrhagic diathesis and cerebral disturbance different from those of the benign catarrhal jaundice. Death occurred eight weeks after the appearance of jaundice. Necropsy, performed by Dr. Kundrat, revealed an enormous dilatation of the common and hepatic ducts which were filled with the same fluid as the smaller intrahepatic ducts. Only the lowest portion of the common duct, about 4 cm. in length, was not distended; its wall was swollen. It was obturated by a polypoid growth of the mucosa, the size of a small pea, situated in the posterior wall 0.5 cm. above the ostium. Beneath it there was a mucous plug. Histologic examination of the polypoid growth revealed a marked proliferation of the mucous glands of the common duct without cell irregularities.

The title of Neusser's paper is misleading because the case reported did not conform with the benign catarrhal jaundice, as emphasized even by the authors. Moreover, necropsy revealed a small but obturating tumor of the common duct. The rather meager histologic report is suggestive of an adenoma of the mucous glands, the mucous plug being the result of their secretory activity. The obstructive jaundice is sufficiently explained by the obturating tumor, the mucous plug, found beneath the neoplasm, without etiologic significance.

CASE 2 (Ryska[55]).—A man, aged 49, an alcoholic patient, died seven weeks after the first appearance of jaundice. Necropsy, performed by Dr. Chiari, revealed the lowest 1 cm. long portion of the common duct occluded by tenacious mucus. The upper part as well as the hepatic ducts, which appeared slightly distended, contained bile. Within the colon there was mushy, acholic fecal matter. The liver was large, 2,025 Gm. There were also evidences of a recent dysentery and an old pulmonary tuberculosis. Microscopic examination revealed hyperemia of the liver. The hepatic cells contain more pigment than usual; they partly show parenchymatous degeneration. A dilatation of the bile capillaries cannot be found. The larger bile ducts are somewhat distended.

It seems to us that the recorded observations at necropsy do not warrant the author's conception of the case as an obstructive jaundice caused by a mucous plug within the common duct. A complete obstruction of the ostium of several weeks' duration always results in marked dilatation of the extrahepatic and intrahepatic bile ducts and microscopic evidence of biliary stasis. The necropsy protocol, however, speaks only of a slight distention of the hepatic ducts and emphasizes that the bile capillaries are without changes. The only evidence in favor of the author's conception is the acholic stools. Observations of French authors have shown the existence of severe jaundice with clay-colored stools but without any obstruction of the biliary passages. Recently a group of similar cases was reported by Symmers.[56] In these cases more or less severe liver changes were found on microscopic examination. The absence of bile pigment within the intestines was explained by the hypothesis of a functional alteration of the liver cells, or, according to Symmers, "was due to inability on the part of the bile to escape from its intrahepatic capillaries since there is no demonstrable obstruction in the larger

54. Neusser, E.: Ein Fall von Icterus catarrhalis mit letalem Ausgang, Ztschr. f. klin. Med. **7**:32, 1884.

55. Ryska, E.: Ein Fall von Icterus catarrhalis mit letalem Ausgang, Prag. med. Wchnschr. **27**:183, 1902.

56. Symmers, D.: Epidemic Acute Hemorrhagic Jaundice of Toxic Origin, J. A. M. A. **74**:1153 (April 24) 1920.

ducts." One is tempted to consider Ryska's case in a similar manner were it not for the presence of bile within the large bile ducts. The inconsistencies in his report do not permit an explanation in one way or the other. Therefore this observation can hardly be accepted as a convincing case of catarrhal jaundice caused by an obstructing mucous plug within the common duct.

CASE 3 (Eppinger[57]).—A girl, aged 19, acquired jaundice after a dietary indiscretion followed by symptoms of a severe gastro-intestinal catarrh. She was

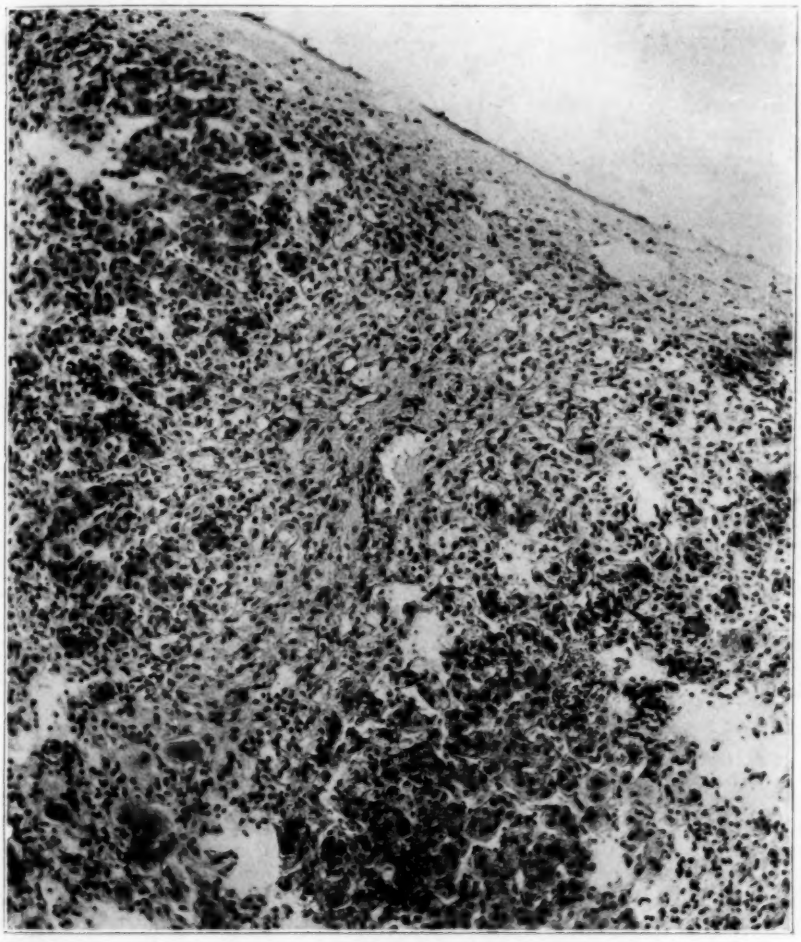

Fig. 1.—Liver lobule with atrophy of the central portion; × 100.

seen eight days later in the dispensary and was admitted to the ward. The next day she committed suicide by leaping from the window. At necropsy the liver was of normal size and icteric; from the large intrahepatic bile ducts, dark, tenacious bile escaped. Within the small intestines were acholic feces. The duodenum also showed whitish contents; its mucosa was swollen and the papilla of

57. Eppinger, H.: Zur Pathogenese des Icterus Catarrh, Wien. klin. Wchnschr. **21**:480, 1908.

Vater distinctly prominent. Even on considerable pressure of the gallbladder no bile escaped from the ostium of the common duct. Histologic examination revealed severe catarrhal changes of the mucosa of the stomach, duodenum and common duct and swelling of the lymphadenoid tissue within the lower part of the common duct.

Eppinger's report is extremely valuable for the problem of the catarrhal jaundice because the death of the patient is merely incidental to the acute icterus. Therefore it is permitted to conclude that the same pathologic condition must exist in other cases with the same clinical symptoms but with the usual benign course. The observation supports the theory of the obstructive mechanism in icterus catarrhalis.

However, Eppinger's next communication regarding the same question shows that the foregoing reported pathologic observations cannot be generally accepted as the morbid anatomy of catarrhal jaundice.

His latest observations concern three cases of icterus in wounded soldiers who died of tetanus. The patients were admitted to the wards together with other men from the same company who also suffered from jaundice. The course of the disease could be followed in the latter, who all recovered after a few weeks without any serious symptoms. Opportunity for anatomic studies was afforded in the three first cases mentioned. In general, the liver showed a diffuse degenerative process with multiple small foci of necrosis. Due to the destruction of liver cells the intracellular bile capillaries were torn. Numerous mitoses were found within the liver cells adjacent to the necrosis.

Eppinger's Classification of Icterus Catarrhalis.—His morphologic observations and clinical considerations have led Eppinger to the following classification of the so-called icterus catarrhalis:

1. Icterus following a severe gastro-intestinal disturbance with apparently perfect liver function but with evidence of a complete bile duct occlusion.

2. Icterus following a severe gastro-intestinal disturbance with alteration of liver function but with presence of bile within the intestines.

3. Icterus generally of type 2 but without a history of a previous gastro-intestinal disturbance.

4. Icterus of type 2 but occurring in the form of small epidemics or endemics.

Comment.—A critical review of the foregoing reports suggests to us the conclusion that only the cases of Eppinger belong to the type of icterus under discussion. Both other observations and the casual remarks on the morbid anatomy of catarrhal jaundice found in other places either pertain to another type of jaundice or the reports are insufficient and therefore without value. Here we are forced to include the observation of Osler,[58] the remarks of Naunyn [16] on chronic catarrhal jaundice in old people and the paragraphs on the pathologic anatomy in most of the text and handbooks.

Our present knowledge of the pathogenesis of the so-called catarrhal jaundice is the result of clinical research. However, the direct morphologic evidence brought forward by the observations of Eppinger is

58. Osler, W.: The Principles and Practice of Medicine, ed. 8, Philadelphia, D. Appleton & Co., 1916, p. 563.

the important check on conclusions which were drawn from the circumstantial evidence of clinical and laboratory experiences.

In view of the scarcity of reports the communication of our clinical and histologic studies in a case of so-called catarrhal jaundice may be permitted.

AUTHORS' CASE

History.—Mrs. Bessie K., aged 40, white, married, admitted Feb. 25, 1925, in the medical service, whose history was of no importance, had had measles when a child. She had never had any other disease until the present illness. She had five living children, and had had no miscarriages. The present illness

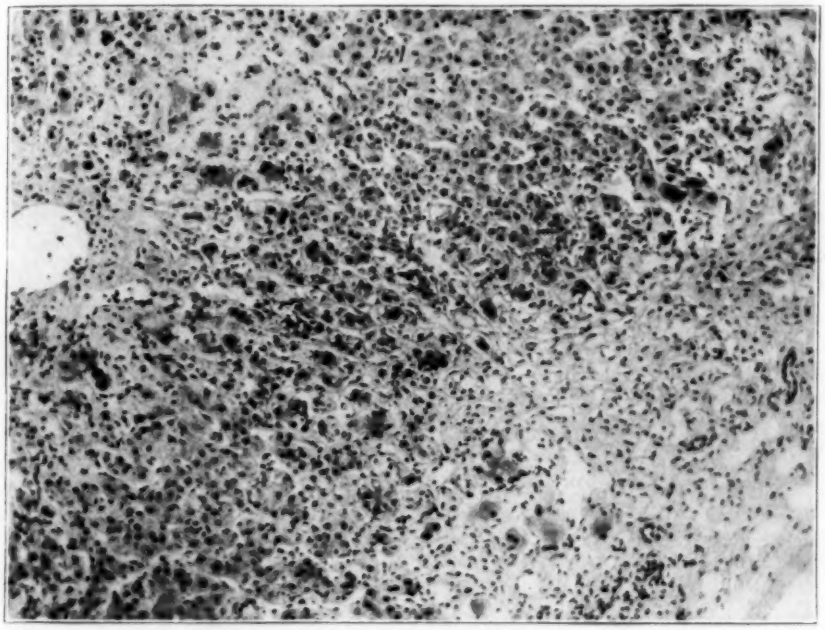

Fig. 2.—Liver parenchyma showing various stages of cellular degeneration and disintegration. Areas of complete cell atrophy with the remaining hepatic framework; × 150.

began one month before admission to the hospital, when the patient, waiting outdoors, had a chill. When she reached home she noticed a rash on her right forearm. This spread over her entire body but disappeared in two days. Following this she began to have pains in her arms, fingers and legs and swelling of these parts. The hand was so swollen that she could not close it. The swelling disappeared in one week, but there was pain in the back like needles, and then all over her body. The physician gave her something to rub on her skin and the pains disappeared. Following this trouble, about three weeks ago, the patient had pain in the epigastrium and on the right side "under my ribs" and in the right lower quadrant. At this time the pain in the epigastrium became very severe at intervals so that she could hardly endure it. A dull pain continued in the epigas-

trium. Following the attacks of severe pain her stools became white, and the jaundice appeared; she vomited only twice.

On admission the patient had intense jaundice and complained of abdominal pain. No pathologic condition was observed in her heart and lungs. The liver was easily palpated 6 cm. from the costal margin in the nipple line; there was tenderness over this area on deep palpation. The temperature on admission was 103.6 F.; it dropped the next day to 102 F., and became normal the following day. Repeated Wassermann reactions were negative. Blood counts were of no significance; coagulation time and bleeding time were prolonged. Stools observed within the hospital were liquid brown. The patient remained until March 4 in the medical department, whence she was transferred to the surgical service of Dr. Charles Gordon Heyd, and an exploratory laparotomy was performed. The liver was about one-third larger than normal. The gallbladder was large, filled with bile. The pancreas appeared normal on palpation. No calculi were determined within the common duct. Cholecystogastrostomy was performed uniting the fundus of the gallbladder to the stomach about 2 cm. proximal to the pyloric ring. A small piece of the liver and of the gallbladder was removed for histologic diagnosis. Two days after the operation the jaundice seemed more intense than it had ever been, but the patient felt much better. After an uneventful recovery from the operation, the patient was discharged on March 19 much improved, but still having jaundice. She was seen several times later in the dispensary, and she is today, more than one year after the operation, in good health.

Histologic Examination.—The lobular structure and the cell cords of the liver were generally well recognizable on low magnification. There were, however, larger and smaller foci scattered throughout the section where the normal hepatic architecture had been lost. They were as a rule poorly defined and their size varied from that of about one-half a lobule to the magnitude of only a few liver cells. Their situation within the lobule varied considerably; the largest foci, however, were found around the central veins (fig. 1). The cell columns were formed by polygonal large cells which showed throughout a coarsely granular cytoplasm. The individual granules stained intensely red with eosin. The nuclei were round with a small amount of chromatin and a large nucleolus. Occasionally, however, there were cells with very large, dark nuclei. Within the continuity of the hepatic cell columns cells could be noticed which were conspicuous by their size. Their cytoplasm showed very large granules and the nuclei were often conspicuously pale. As long as such cells were only interspersed between the cell cords their continuity was not interrupted. Yet there were numerous larger and smaller cell groups in which the majority of the cells showed the structural alterations mentioned above (figs. 2 and 3). Closer examination with high magnification revealed cells within most of the foci with a hyaline meshwork in the cytoplasm. The cell membrane was mostly indistinct and interrupted, often adjoining cells becoming fused because of the complete disappearance of the cell membrane. Generally such cells showed nuclear changes of the type of karyolysis, starting with loss of the nucleolus and ending with complete nuclear disappearance (fig. 5). Occasional necrotic cells were surrounded by polymorphonuclear leukocytes. Frequently shrunken and disintegrating cells were found within the foci (figs. 2 and 3). Here the capillaries were wide, the fibrillar framework was conspicuously coarse and numerous polymorphonuclear leukocytes, lymphocytes and large mononuclear cells accumulated within the gaps caused by the cellular destruction. Larger and smaller foci showed only the fibrillar framework of the liver with the capillaries and numerous lymphocytes

(figs. 1 and 2). Spindle-shaped endothelial cells were found within the capillaries in varying numbers. They often showed a vacuolized cytoplasm with a kidney-shaped nucleus. Numerous round cells with identical nucleus were found within the larger and smaller branches of the hepatic vein. In the vicinity of the focal cell destruction very large cells with from 2 to 5 nuclei were found. The cytoplasm around the centrally grouped nuclei showed the coarse cytoplasmic granulation to a marked degree (fig. 4). Mitotic division figures were rare, but amitosis was more frequent. Liver cells with vacuolized cytoplasm were rare. Sudan stain did not reveal fat within the cells. Best's carmine stained all the cells faintly pink; only occasionally red granules were found. Bile pigment was found within necrotic cells in the form of brown granules, rarely as bile casts. The bile capillaries were generally straight, narrow and sharply outlined. Within the foci of cell destruction, however, they were mostly tortuous and varicous and occasionally ruptures of the minute ducts were found (fig. 6). The perilobular

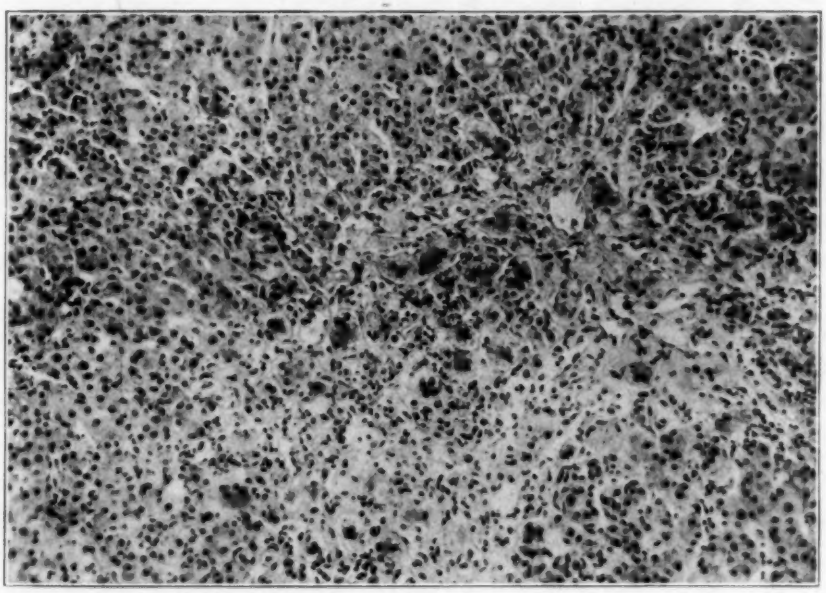

Fig. 3.—Area similar to that in figure 2. Note the numerous large hepatic cells with the coarse granular cytoplasm; × 160.

connective tissue fields often showed infiltration with polymorphonuclear leukocytes and lymphocytes. The ramification of the portal vein and hepatic artery were without changes. Throughout the bile ducts were empty, their epithelial lining regular, high columnar, and there was no infiltration of the tissue around.

COMMENT

Before entering on a detailed discussion, it seems correct to state in brief the reasons why we consider the case as one of the so-called icterus catarrhalis group.

The history, the lack of severe constitutional symptoms and cutaneous hemorrhages, the absence of renal symptoms and splenic tumor

permit one to rule out Weil's disease. The sudden onset of the jaundice, its benign course and the absence of clinical and even bioptic evidence of cholelithiasis are the three points requested by Eppinger's definition for the diagnosis of catarrhal jaundice. Yet we are conscious of the fact that this term has been applied for a number of morbid entities widely differing in their symptomatology, pathogenesis and etiology. It is the purpose of this paper to attempt to separate these different types of acute benign jaundice.

The leading clinical symptom in our case is the icterus of several weeks' duration, neither preceded nor accompanied by symptoms of gastro-intestinal disturbance. However, it was ushered in by an attack of articular pains and swellings of more than a week's duration. Articular rheumatism in its relation to so-called catarrhal jaundice was first mentioned by Graves,[4] who spoke about eight cases of his observation. Later writers, however, did not pay attention to his observations. Strisower [17] observed six cases of jaundice starting with the symptoms of joint rheumatism which he considered cholangitis. (See our discussion in the first part.) Loewenhardt [59] reported one case of icterus following a recurrence of chronic articular rheumatism. Anhemolytic streptococci were found in the blood. Marcou-Mutzner [60] mentions three cases of jaundice with initial symptoms of articular pains which he conceives as symptoms of an anaphylactic shock. Felsenreich and Satke refer to one case. Since our attention was attracted to that relationship, we have had the opportunity of observing another almost similar case.

A woman, aged 26, unmarried, on Feb. 12, 1926, developed a rash extending over the dorsal sides of both forearms and legs. It was diagnosed as erythema multiforme and the patient was cautioned to stay in bed because of the probability of a subsequent articular rheumatism. The rash disappeared within a few days, but was immediately followed by severe pains in both shoulders, elbows, wrists and ankles with only slight swelling of the wrists. The temperature was about 100 F. The patient was treated with large doses of sodium salicylate and rest in bed. The symptoms disappeared within two weeks, and the patient was allowed to return to work on March 1. She was seen again on March 4, when her sclerae showed a faint yellow tint. She reported that her urine had been dark for several days. Previous symptoms of a gastroduodenal disturbance were entirely absent, and also during the course of the jaundice only occasional nausea was complained of. The jaundice became very deep within the next few days, and pruritus was intense for several days. The stools were clay colored for one week with two days' intermission, when they became yellow. There was marked tenderness of the liver, which was found two finger breadths below the sternocostal margin. The spleen was not palpable. Only a few times was the temperature near 100 F.; it was mostly normal. The jaundice cleared up within eighteen days and had disappeared fully five weeks after onset. The patient was treated at her home, and therefore no laboratory examinations were made. The subsequence

59. Loewenhardt: Klin. Wchnschr. **3**:192, 1923.
60. Marcou-Mutzner: Presse méd. **33**:1286, 1925.

of the symptoms and the identity of both cases points more to a causal relationship between the articular rheumatism and the jaundice than to a mere coincidence.

In both of our cases as well as in the six cases of Strisower's observation the absence of preceding gastro-intestinal disturbances rules out a mechanistic explanation of the jaundice. No other infectious disease preceded the icterus but the articular rheumatism. These facts and their critical consideration are no doubt sufficiently conclusive to consider the icterus in our case as of hematogenous origin. Jones and Minot [21] report an increase of the mononuclear cells of the blood in infectious jaundice. The examination of the blood in our case did not reveal anything abnormal. However, the histologic examination revealed an excessive number

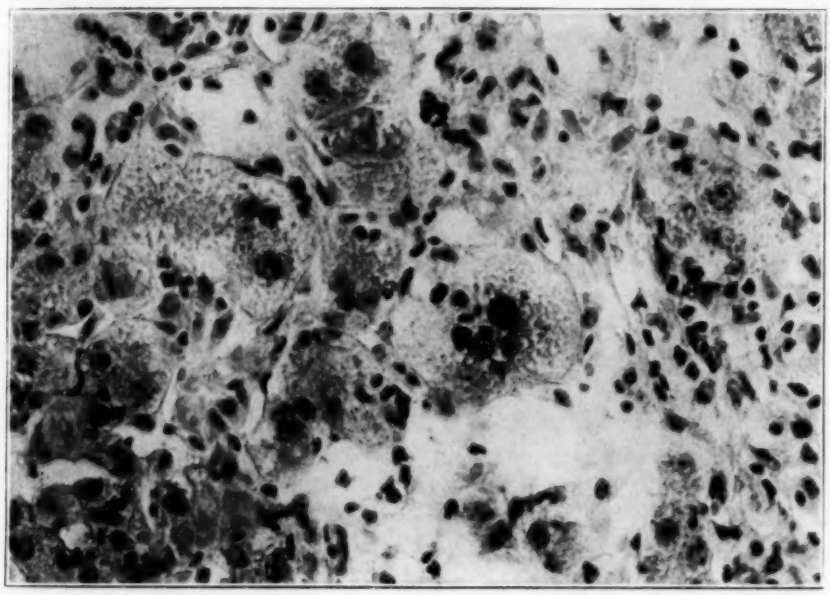

Fig. 4.—Large liver cells with granular degeneration and one with numerous nuclei; × 700.

of large mononuclear cells within the hepatic veins and desquamation of proliferated Kupffer's cells. Cirrhotic processes as the result of so-called catarrhal jaundice were reported by Eppinger,[1] Jones and Minot [21] and Ewstatiew.[61] The patient under our observation has remained free from further symptoms up to the present, fourteen months after the disease.

In table 1 are presented the results of the tests for bilirubin of the blood serum and urobilin in the urine in three cases of catarrhal jaundice. Bernheim's technic [62] for the icterus index was utilized, and since its

61. Ewstatiew: Jahrb. f. Kinderh. **33**:199, 1922.
62. Bernheim, A. R.: Icterus Index, J. A. M. A. **82**:291 (Jan. 26) 1924.

introduction McMaster's quantitative method [63] for urobilin in the urine. Before McMaster's method was available, the iodine test of Gerhardt or the alcoholic zinc chloride test of Wirsing was used. In the cases presented in the table, a hyperbilirubinemia is accompanied by a marked output of urobilin in the urine. In the first instance 148 mg. of urobilin were excreted per hundred cubic centimeters of urine, with an icterus index of 46. When the icterus index had decreased to 27, the urobilin output dropped to 94 mg. per hundred cubic centimeters. At the height of the hyperbilirubinemia, both the direct and indirect van den Bergh

TABLE 1.—*Bilirubin of Blood and Urobilin of Urine in Catarrhal Jaundice*

Case	Age	Sex	Time, Days	Icterus Index	van den Bergh		Urobilin, Mg. per 100 Cc. of Urine
					Direct	Indirect	
1. M. J.	35	F	..	46	+++	+++	148
			44	27	0	+	94
2. H. M.	8	F	..	151	++++	++++	++
			12	155	++++	++++	++
			12	93	+++	+++	
			21	28	0	+	
3. E. S.	21	F	..	105	++++	++++	+
			5	63	++	+++	

TABLE 2.—*Chemical Changes in the Blood in a Case of Catarrhal Jaundice (B. K.).*

Time	Icterus Index	van den Bergh		Non-protein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen		Amino Acid Nitrogen, Mg. per 100 Cc.	Uric Acid, Mg. per 100 Cc.	Sugar, Percentage	Cholesterol, Percentage	Fibrin, Percentage
		Direct	Indirect		Urea Nitrogen, Mg. per 100 Cc.	Non-protein Nitrogen, Mg. per 100 Cc.					
2/27/25	225	++++	++++	31.9	8.3	0.26	7.2	1.5	0.106	0.160	0.340
3 days	220	++++	++++	....	....	....	...	...	.....	.....	.....
8 days	80	++	++	33.0	13.7	0.41	6.5	1.5	.....	.....	.....
8 days	52	++	++	22.4	7.5	0.34	7.0	2.6	.....	0.166	0.340
8 days	35	—	+	....	....	....	...	...	.....	.....	.....
33 days	11	—	+	30.0	12.5	0.41	...	1.8	.....	.....	.....

reactions are strongly positive. However, with a diminishing icterus, the direct reaction first becomes negative, usually when the icterus index falls below 30. The indirect reaction remains positive until the icterus index has reached 10 or below.

Data on the tests for hyperbilirubinemia and chemical changes in the blood on B. K., the subject of the report, are presented in table 2. On admission the icterus index of the blood serum was 225 associated with strongly positive direct and indirect van den Bergh reactions. There is observed a steady decrease in the bilirubin of the blood serum. After

63. McMaster: J. Exper. Med. **41**:503, 1925.

thirty-three days the icterus index has dropped to 11. Here again it is observed that with a diminishing hyperbilirubinemia, the direct van den Bergh reaction becomes negative before the indirect. The indirect reaction remains positive when the icterus index has reached 11. We cannot here enter into a discussion of the significance of these reactions beyond the statement that in a future communication a comparison of the relative value of tests for hyperbilirubinemia will be presented in detail. At the height of the icterus, the patient showed a large amount of urobilin in the urine. Wallace and Diamond,[64] in their exhaustive study of

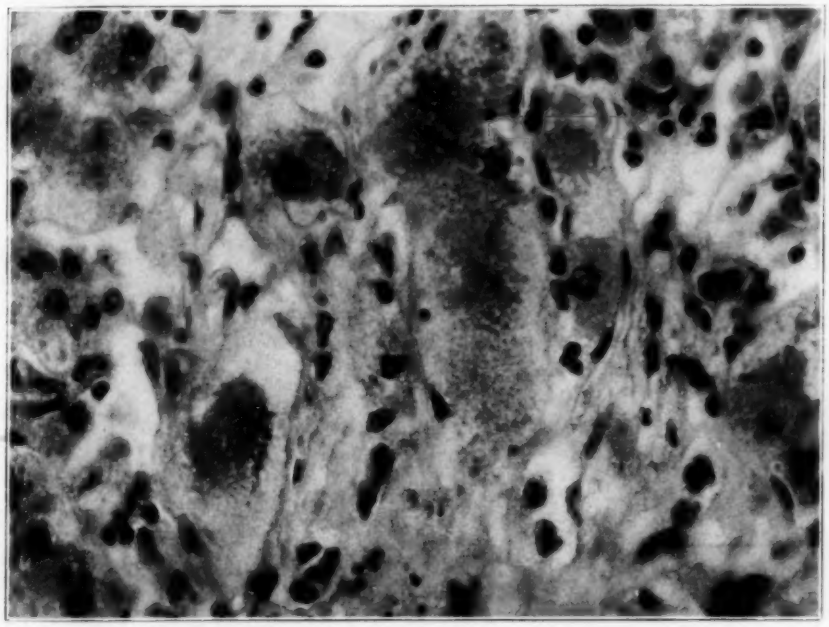

Fig. 5.—Liver cells showing the granular degeneration and various stages of karyolysis ending with complete nuclear disappearance; × 800.

the urobilinogen and urobilin in liver and gallbladder disease, found these present constantly in the urine in catarrhal jaundice.

Although the figures for the nonprotein nitrogen content of the blood are within the limits considered physiologic, the urea nitrogen is proportionately low. Hence the ratio of the urea nitrogen to nonprotein nitrogen is below 0.45. At the time the icterus index had reached 225, this ratio was 0.26. At this time the urea nitrogen formed but 25 per cent of the nonprotein nitrogen, indicating a corresponding increase in the rest

64. Wallace, G. B., and Diamond, J. S.: Significance of Urobilogen in Urine as a Test for Liver Function, with a Description of a Simple Quantitative Method for its Estimation, Arch. Int. Med. **35**:698, 1925.

nitrogen. Since there is no direct means of determining the rest nitrogen of the blood, the calculation of this ratio is of considerable practical importance. The significance of the ratio has been emphasized by Chesney, Marshall and Rountree, Whipple and Van Slyke,[65] Killian and Sherwin,[66], Killian,[67] Heyd, Killian and MacNeal,[68] and Standler.[69] Chesney, Marshall and Rountree regard a urea nitrogen percentage of nonprotein nitrogen less than 40 as abnormal; however, we believe a figure less than 45 for the resting and fasting state as the lower physiologic limits.

Greene, Sandiford and Ross[70] state that the amino acid nitrogen in blood varies between 4.8 and 7.8 mg. per hundred cubic centimeters, the average being 6.3 mg. This statement is based on 400 observations covering 20 pathologic conditions. Increases in the amino acid nitrogen of the blood were noted in leukemia and acute yellow atrophy of the liver. Van Slyke[71] remarks that the more the problem is studied with quantitative methods, the more it appears that the liver injury must be

TABLE 3.—*Icterus Index of Blood and Dye Retention in Catarrhal Jaundice*

Case	Time, Days	Icterus	Percentage of Dye in Blood Serum	
			15 Minutes	60 Minutes
1. E. S.	..	105	20	20
	5	62	14	20
	12	30	12	15
2. B. K.	..	225	15	20
	10	80	7.5	10
	8	52	0	4
	8	35	5	0
	33	11	5 (—)	0

extreme before it can cause an unusual accumulation or excretion of amino acid. All of the figures for the amino acid nitrogen are within the limits considered normal. In this respect there is a striking contrast with the observations for acute yellow atrophy of the liver and fatal phosphorus poisoning. Considering the average normal figures for Benedict's method, the uric acid of the blood is low. The sugar, cholesterol and fibrin are all normal.

In table 3 data on the icterus index of the blood serum and the results of the Rountree-Rosenthal dye test for liver function are presented for

65. Whipple and Van Slyke: J. Exper. Med. **28**:213, 1918.

66. Killian and Sherwin: Am. J. Obst. Gynec. **2**:6, 1921.

67. Killian: Toxemias of Pregnancy, Philadelphia, D. Appleton & Co., 1922.

68. Killian and MacNeal: The Liver and Its Relation to Chronic Abdominal Infections, St. Louis, C. V. Mosby Company, 1924.

69. Standler: Bull. Johns Hopkins Hosp. **35**:133, 1924.

70. Greene, Sandiford and Ross: J. Biol. Chem. **58**:845, 1923.

71. Van Slyke: Principles of Pathologic Histology, Philadephia, W. B. Saunders Company, 1920.

two cases of catarrhal jaundice. Case 2, B.K., is the subject of the present report. Shattuck, Browne and Preston have reported a comparative study of some of the newer and more promising tests for liver function. Their results appear to indicate that the icterus index is the most useful single liver functional test for clinical work. The dye test is a supplementary test in measuring liver function, having its greatest value in the diagnosis of liver disease in patients without jaundice. Rosenthal [44] has produced experimental evidence to show that the removal of phenoltetrachlorphthalein from the blood serum furnishes an index of hepatic function that is quantitative. The results obtained depend

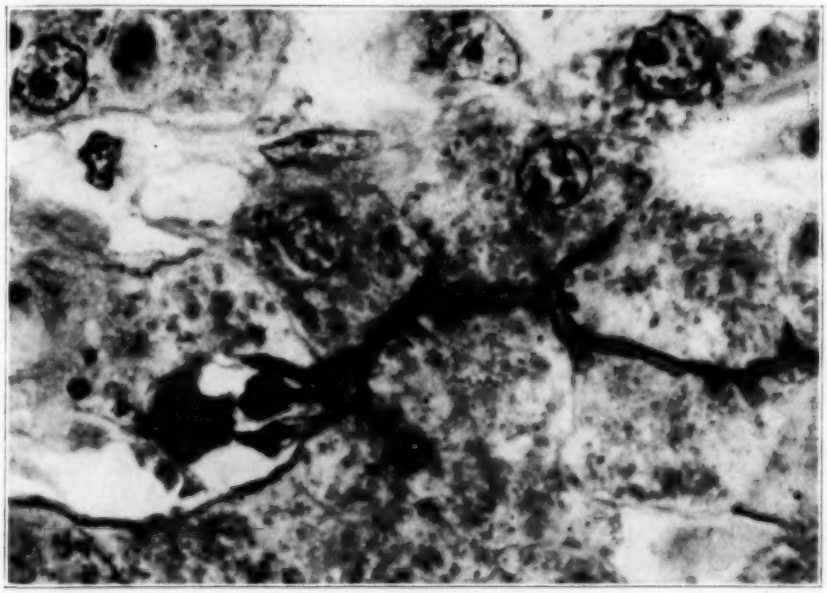

Fig. 6.—Rupture of intracellular bile capillary with extravasation of bile: × 1,400.

primarily on the condition of the liver cells, and there exists a close relation between the quantity of normal liver tissue and the excretion of the dye. In the cases reported in the table there is observed dye retention in the blood serum. The sixty minute specimen of serum shows an equal or greater concentration of the dye than does the fifteen minute specimen at the height of the jaundice. In the second instance the dye test returns to normal, when the icterus index is 35, and when the icterus index had dropped to 11, a normal dye reaction is also obtained. From a comparison of these results it appears that the liver function is restored to normal, as judged by the dye test, before the concentration of bilirubin in the blood has been diminished to its normal concentration.

The outstanding feature in the microscopic picture is the diffuse granular appearance of the liver cells and the multiple foci of cell destruction. Aside from the granular degeneration, we observed a form of cytoplasmic alteration which Mallory [71] described as hyaline degeneration, ordinarily found in alcoholic cirrhosis. The importance of these protoplasmic changes for the cellular vitality is evidenced by the scattered foci of necrobiosis and necrosis. Here one cannot fail to detect side by side cells with granular degeneration, others with a wide range of forms of nuclear disintegration and finally some with complete disappearance of the nucleus. Therefore the morphologic picture indicates the serious character of the cell damage and explains the severe functional alteration in our observation.

Among the foci of cell destruction we distinguish those in which the necrosis is still recent and those composed of only the reticular framework of the liver and the proliferated endothelial cells. It is evident that the latter foci are older than the others. It proves that the cell destruction had already set in during the first weeks of the jaundice.

Our histologic observations parallel the observations of Eppinger except for a few details. Mitotic figures like those he reported were not detected, but there were numerous very large liver cells with several nuclei. We considered them the result of amitotic nuclear division without cell division, a frustrated attempt at regeneration.

On the strength of his morphologic data, Eppinger concludes that the liver changes in acute yellow atrophy differ only in degree from those of his observations in benign icterus. He maintains [72] that "severe cases of acute catarrhal jaundice are forms of acute atrophy of the liver 'en miniature.'" Our observation supports his statement as far as the histologic picture is concerned, and some histologic details may add further proof.

The extensive lobular necrosis with karyolysis is the outstanding feature of the liver in the recent stages of acute yellow atrophy. One is tempted to conceive the cell necrosis as the result of a primary nuclear destruction because the cytoplasmic outline is frequently intact while the nucleus has disappeared. Anschütz [73] and Paltauf [74] have emphasized the contrast in the development of cell necrosis in acute yellow atrophy and phosphorus poisoning, namely, the primary nuclear destruction in the first and the primary cytoplasmic alteration with subsequent cell necrosis in the latter condition. The histologic examination in our

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71. Mallory: Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1920.

72. Eppinger: Verhandl. d. deutsch. path. Gesellsch. **18**:272, 1921.

73. Anschütz: Arb. a. d. path. Inst. zu Tübingen **3**:230, 1902.

74. Paltauf: Verhandl. d. deutsch. path. Gesellsch. **5**:91, 1903.

observation indicates a primary injury of the cytoplasm with subsequent karyolysis as the modus of the focal cell necrosis. The gradual necrobiosis found in our case contrasts with the picture of complete nuclear loss commonly found in acute yellow atrophy. If we conceive the extensive cell necrosis of that condition as the result of a sudden primary injury on the nuclei, then certainly the microscopic picture of our observation would essentially differ from that of acute yellow atrophy. Yet the validity of such a conception must be questioned on the strength of Umbers, Fränkel's and Hanser's observations. According to Umber,[75] the liver in acute yellow atrophy, as found at necropsy, is only a postmortal product of autolysis (postmortales Verdauungs product) of the living organ. He bases his opinion on the difference in the appearance of the liver in the operating room and at the necropsy table. This extreme standpoint was refuted by Fränkel,[76] who also had the opportunity to compare, histologically, the liver antemortem and postmortem in two cases. He believes that the necrosis evidenced by the nuclear disintegration is vital although the intensive postmortal autolysis may help to exaggerate the picture. Hanser [77] sides with Fränkel in the attempt to disprove Umber's opinion, but his photomicrographs demonstrate the great contrast between the antemortem and postmortem picture in a recent case of acute yellow atrophy. His pictures and description indicate that the nuclear disintegration was not found before death to such an extent as observed in the necropsy material. The conspicuous difference cannot be attributed to the time (six hours) which had elapsed between the time of the operation and death. It necessitates a revision of the conception regarding the development of the widespread cell necrosis in acute yellow atrophy. We conceive the cell necrosis in that condition as the termination of a severe degenerative process of the cytoplasm as indicated by the picture of Hanser and not as the result of a sudden nuclear death. The same modus of development, however, could be recognized in the liver in our case. The identity of picture 2 of Hanser's paper with our picture 4 fully supports the contention that the morphologic changes in acute yellow atrophy and our case of so-called catarrhal jaundice are essentially identical.

Another histologic feature supporting that conception is well illustrated in figure 1. The picture of the older foci of cell destruction compares well with the red portions of a subacute liver atrophy of several weeks' duration.

It is not the purpose of this paper to theorize about the mechanism of the jaundice in the different forms of so-called icterus catarrhalis,

75. Umber: Deutsche med. Wchnschr. **45**:537, 1919.

76. Fränkel, E.: Deutsche med. Wchnschr. **46**:225, 1920.

77. Hanser: Verhandl. d. deutsch. path. Gesellsch. **18**:263, 1921; Virchows Arch. f. path. Anat. **233**:150, 1921.

but it seems evident that in the case under our observation the icterus was due to the multiple rupture of bile capillaries. This statement is supported by the presence of bile within the gallbladder and intestines which rules out an obstructive mechanism, the direct van den Bergh test which points to an hepatic origin and lastly the direct morphologic evidence. We are conscious, however, of the fact that the mechanism of the icterus might have been different at another phase of the disease. The biphasic van den Bergh reaction at the beginning and at the end of cases of catarrhal jaundice as reported by Lepchne, Strisower, Shattuck and also observed by us in this case and others may require a different explanation. The same holds for Brulé's observation of periods of dissociation in so-called catarrhal jaundice.

CONCLUSIONS

The so-called "icterus catarrhalis" is neither a morbid nor a pathologic entity. Three forms can be differentiated:

1. Icterus due to obstruction of the common duct following gastrointestinal catarrh—true catarrhal jaundice.

2. Icterus due to degeneration and multiple necrosis of the liver, hematogenous in origin.

3. Icterus due to cholangitis, mostly of hematogenous origin.

The etiologic factor of group 2 is not known; bacterial toxins of various types have to be considered. It is probable that in group 3 atypic strains of *B. paratyphosus* are of etiologic importance. It is possible that groups 2 and 3 frequently merge with each other.

The evidence of hepatic derangement in cases of group 2 suggests careful observation of these cases and dietary regulations in order to prevent further damage to the liver. The history, the presence of urobilin in the urine and the positive results of practically all the liver function tests permit a differentiation from group 1. Further studies are necessary, however, in order to make a correct differentiation of groups 2 and 3 possible.

PRIMARY ACUTE AORTITIS *

B. Z. RAPPAPORT, M.D.

CHICAGO

The term "primary acute aortitis," as used here, is applied to acute inflammations of the aorta in which the infection is not attributable to an associated or preceding infection of the heart valves or of the adjacent mediastinal structures. The condition is so rare that Stumpf [1] in an exhaustive review enumerated, in addition to his own, nine other reported cases. The following case is reported not only because of the rarity of the condition, but also because of the association of an acute with a syphilitic infection of the aorta.

REPORT OF A CASE

History.—A man, aged 47, in Dr. C. S. Williamson's service, complained of cough, dyspnea, swelling of the feet, and numbness and coldness of the extremities. These symptoms, while present for years, had become more marked during the last eighteen months. Sudden paroxysmal attacks of dyspnea associated with great anxiety had also recurred with increasing severity in this period. He had fallen five months before admission, bruising the left side of his chest. Hemoptysis had been present for forty-eight hours before admission. He said that he had had a syphilitic infection twenty years previously.

Physical Examination.—This revealed cardiac decompensation. Cyanosis of the face and of the mucous membranes was present. Harsh breath sounds and râles were heard over the bases of the lungs, more marked on the right side. There was a visible, diffuse precordial impulse, palpable in the sixth interspace 11 cm. from the midsternal line. The left heart border was 11 cm. from the midsternum; the right was not percussable. The heart tones were distant, with a systolic murmur at the apex transmitted to the axilla and a diastolic murmur over the lower part of the sternum. The pulse was equal at the radials and full, approaching a Corrigan type. The blood pressure was systolic 175, diastolic 70. The liver was palpable two fingerbreadths below the costal margin. No fluid was demonstrable in the abdomen. The lower extremities were edematous, the reflexes normal.

Laboratory Examination.—The blood Wassermann reaction was strongly positive. The blood nonprotein nitrogen was 50 mg., the sugar 94, and the carbon dioxide combining power 48.5 per hundred cubic centimeters. The chest plate revealed transverse cardiac enlargement. The urine contained a large amount of albumin, and hyaline and granular casts. The phenolsulphonphthalein excretion was 87 per cent in three hours. The white count was 5,300, the red blood count, 4,750,000, the hemoglobin 90 per cent.

Course of Illness.—The temperature remained normal throughout his stay in the hospital. Seventeen days before death he suddenly complained of severe pre-

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* From the Department of Pathology and the Research and Educational Hospital of the University of Illinois.

1. Stumpf: Beitr. z. path. Anat. u. z. allg. Pathol. **56**:417, 1913.

cordial pain, became greatly cyanosed, dyspneic, and had chilly sensations which were followed by profuse sweating. The attack recurred the next day. The pulse rate was 120, the respirations 40 per minute. Venesection was performed, and after 550 cc. of blood was removed, the symptoms subsided. There was another attack associated with a chill, which was followed by profuse hemoptysis and precordial pain. The patient became delirious two days before death.

Necropsy.—Necropsy was performed by Dr. R. H. Jaffé six hours after death. The following is a summary of the record:

The body was that of a well nourished man weighing 175 pounds (79.4 Kg.). There was slight edema of the ankles. The abdomen contained 1,000 cc. of a clear, yellow fluid. Both lungs were firmly attached to the thoracic wall. They

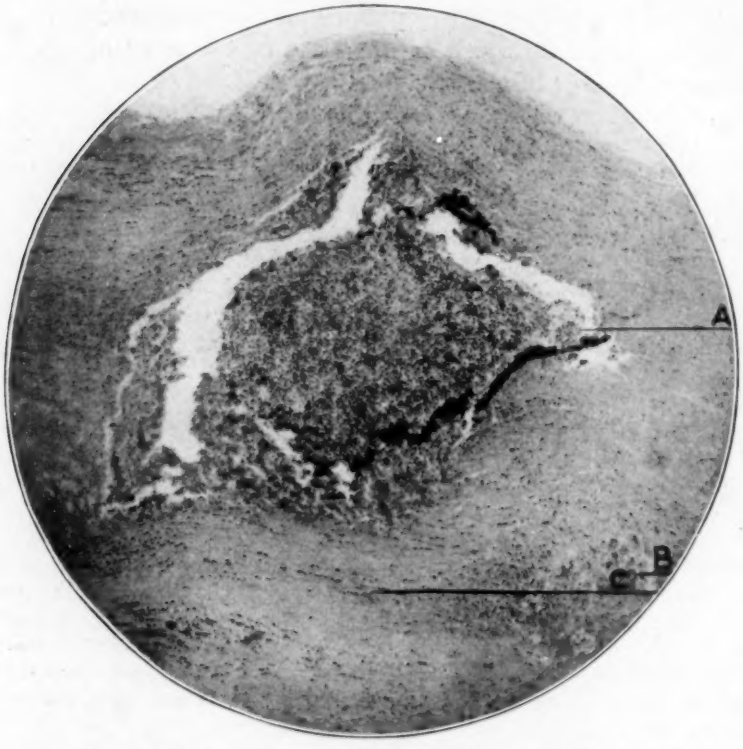

Fig. 1.—*A*, indicates the subintimal miliary abscesses bulging the intima toward the lumen of the vessel; *B*, focal necrosis of media with polymorphonuclear infiltration; *C*, streaks of polymorphonuclear cells between the lamellae of the media; hematoxylin and eosin stain; × 60.

contained air in all parts except in a wedged-shaped portion at the anterior margin of the left upper lobe. This was firm, and on section, dark red. The heart weighed 780 Gm., the wall of the left ventricle being 25 mm. in thickness, that of the right 10 mm., and the cross diameter of the left chamber 14 cm. The myocardium was reddish brown, firm and rubbery. The endocardium was white, the trabeculae thickened. The aortic cusps were smooth, with no change except a slight thickening of the free margin of the anterior cusp. There was, however, no evidence of either old or recent endocarditis. The right auricle

contained firm, dark red blood clots, and a thrombus of similar appearance was present in a branch of the left pulmonary artery leading to the area of infarction. The aorta above the valve was 82 mm. in circumference. There were many longitudinal depressions in the pars thoracica. The openings of the coronary arteries, especially of the right, were narrowed. Just above the aortic cusps were five light yellow, slightly elevated plaques, from 2 to 3 mm. across, resembling atheromatous areas, but sufficiently different to attract particular attention. The aortic wall, including these plaques, was taken for microscopic study. The spleen weighed 210 Gm. and was filled with blood. The mucosa of the stomach was dark red and covered with mucus. There were fresh hemorrhages in the mucosa of the pelvis of the right kidney. The liver weighed 1,380 Gm. The centers of the lobules were more distinct than normal. The mucosa of the intestines was slightly swollen, grayish red and covered with mucus.

Cultures from the heart blood revealed short chained gram-positive streptococci. A narrow green zone was present about each colony on blood agar after forty-eight hours' incubation.

Microscopic Examination.—Sections of the aorta taken through the yellowish plaques previously mentioned revealed in the intima and between media and intima circumscribed areas of homogeneously staining, granular material in

Fig. 2.—Gram-positive cocci in a subintimal abscess; *A*, in chain arrangement; *B*, diplococcus; Gram-Weigert stain; × 1,200.

which were found round cells with segmented nuclei. The intima in some of these places bulged forward into the lumen of the aorta (fig. 1), and was at some points completely ruptured, permitting the cavities to communicate with the lumen of the vessel. Extending in streaks from these cellular infiltrations between the layers of the intima, as well as into the media, were polymorphonuclear leukocytes in a granular, necrotic substratum. The elastic fibers in and about the areas of infiltration were broken up or completely destroyed. Here and there an irregular segment of an elastic fiber was found in the midst of a polymorphonuclear cell cluster.

In addition to these acute changes, there was also evidence of chronic inflammation. The intima was hyalinized and thickened, forming in some places flat, elevated plaques. The media in its external two thirds revealed no polymorphonuclear leukocytes. Thin-walled, branching, newly formed vessels were found here, surrounded by groups of round plasma cells. The adventitia was greatly thickened and hyalinized. Its vessels were thick-walled, engorged with blood and surrounded by round and plasma cells.

With the Gram-Weigert stain, gram-positive diplococci and cocci in chains were present in the miliary abscesses of the intima previously described (fig. 2). A search for spirochetes by Levadati's method failed to reveal any in sections from the aorta or from the organs studied.

With sudan III, coarse, fat droplets and fat filled large monocytes were demonstrable about the periphery of each polymorphonuclear cluster. Within each abscess, however, only a few fat droplets or fat laden cells were found. Fine, powdery fat droplets were also present in the rest of the intima and slightly coarser ones diffusely in the media.

In and about the newly formed vessels of the media, among plasma and round cells, were round, highly refractile, gram-positive bodies, from two to three times the size of a lymphocyte, which was an unusual observation. These bodies appeared to be hyaline bodies similar to those described by Russel in cases of carcinoma of the stomach (Russel or fuchsin bodies). These are now usually regarded as degenerated plasma cells.

The muscle fibers of the heart were hypertrophied. Their nuclei stained deeply with hematoxylin and varied greatly in size and shape, some being bent, others notched or irregularly twisted with brown lipopigment present about them. There was an increased amount of slightly edematous connective tissue and small infiltrations of round cells and polymorphonuclear leukocytes about the vessels. In the centers of the liver acini, the sinuses were distended with blood, the liver cells were atrophic and filled with fat droplets and brown pigment, while about the periphery of the acini the liver cells were normal in appearance, clear, with relatively small vesicular nuclei and single small fat droplets. These peripheral cells were free from pigment (newly formed liver cells). The Kupfer cells at the periphery were filled with fat, while those at the center were free from fat. There was an increased number of periportal round cells.

The glomerular tufts of the kidney were distended with blood, and their basement membrane, as well as that of Bowman's capsule, was thickened. A few of the glomeruli had undergone hyaline change. Fine fat droplets were present in the cells of the tubuli contorti and in those of the collecting tubules. The lumina of the latter were often filled with hyaline, albuminous material. There was hyaline thickening of the interstitial tissue of the medulla. The larger arteries were unchanged.

The sinuses of the spleen were distended with blood, the follicles were small, and there was sclerosis of the arteries. Many of the reticulum cells of the follicles contained fat droplets. No fat was present in the cells of the pulpa.

COMMENT

The case described is one of primary acute aortitis, since no mural or valvular endocarditis was present. The origin of the infection was not determinable as the necropsy was limited to an examination of the thoracic and abdominal viscera. In previous cases,[2] the primary site of infected varied greatly, an infected carcinoma of the uterus in one case [3] sepsis following the removal of a lymphosarcoma in another,[3] a preceding pneumonia in a third,[4] and a chronic cystitis in a fourth case.[3]

The causative organism here is a streptococcus of the viridans group, demonstrable both culturally and in stained sections. Cocci have been found in two other cases, a staphylococcus by Stumpf [1] and a

2. Barbacci, also Buhl-Mayer, quoted from Stumpf (footnote 1). Vanzetti: Centralbl. f. allg. Pathol. u. path. Anat. **19**:984, 1909.

3. Barbacci, also Buhl-Mayer, quoted from Stumpf (footnote 1).

4. Vanzetti: Centralbl. f. allg. Pathol. u. path. Anat. **19**:984, 1909.

pneumococcus by Vanzetti.[4] Riecker [5] recently reported a case of chronic aortic endocarditis with acute aortitis in which a positive gonococcus culture was obtained before death. Beneke [6] describes a case of chronic, proliferative inflammation of the aorta, that he attributes to a healed phlegmonous aortitis due to *Streptococcus hemolyticus* found in the recent influenza epidemic. It is noteworthy that even the anthrax bacillus has been found [7] as a cause of acute aortitis.

The mode of transmission of the infection may be one of two routes, either through the vasa vasorum or by direct implantation. The first of these routes is favored by MacCrae,[8] by Schauer [9] and by Stumpf.[1] All of these authors emphasize the importance of the lowered local resistance of the vessels due to sclerosis or chronic inflammation. The other mode of transmission, that of direct implantation, seems to be the one most probable in this case as suggested by the marked changes localized to the intima or immediately below it. This route presupposes, even more than the other, the presence of change in the smoothness of the intima or swiftness of the current. The occurrence of infection in the presence of obstruction to the current is most clearly brought out in cases associated with congenital anomalies.

Buchwald and Hart [10] report the presence of polypoid excrescences around the opening of a patent ductus arteriosus following an acute verrucous mitral endocarditis. Marchand [11] and Richter [12] emphasize the importance of local change of the aorta due to previous atheromatous processes as predisposing to acute inflammation. The presence of the depressed scars caused by the syphilitic process in this case is considered an important influence in the localization of the infective material as well as the development of the inflammation due to a lowered resistance of the vessel wall.

From a histologic point of view several details should be emphasized: First, the miliary abscesses under and in the intima are inflammatory and not of atherosclerotic origin. The presence of the cocci and the fatty changes about the periphery rather than in the center of the abscesses bear out this conclusion. It is also noteworthy in this case, the first one reported of an acute associated with a syphilitic aortitis, that the recent process had no influence on the histologic details of the

5. Riecker: Am. Heart **1**:191, 1925.
6. Beneke: Virchows Arch. f. path. Anat. **254**:723, 1925.
7. Oliver: Lancet **2**:1033, 1891.
8. MacCrae, quoted from Stumpf (footnote 1).
9. Schauer: Berl. klin. Wchnschr. **15**:666, 1910.
10. Buchwald and Hart, quoted from Stumpf (footnote 1).
11. Marchand: Eulenburg's Realencyclopädie, ed. 3, **2**:222.
12. Richter: Ueber die Beteiligung der Aorta an endocarditischen Prozessen, Kiel, 1891.

syphilitic changes. The absence of spirochetes in the infiltrations of round cells and polymorphonuclear leukocytes in the myocardium is important. The round cells may be attributable to the syphilitic infection. The presence of polymorphonuclear leukocytes, in view of the changes of the aorta and the septicemia present, may well be attributed to the invasion of streptococci, although these, like the spirochetes, were not demonstrable in stained sections. Warthin,[13] on the other hand, reports eight cases of sudden death in which, together with round and plasma cells, infiltrations of polymorphonuclear leukocytes were found in the myocardium. He found spirochetes in the sections. The finding of polymorphonuclear leukocytes, together with the history of sudden death, is interpreted by this author as evidence of an acute exacerbation of a latent syphilis. No mention is made of other bacteriologic observations in these cases.

SUMMARY

A case of primary acute aortitis due to *Streptococcus viridans* is reported, with no aortic endocarditis present. A syphilitic aortitis was associated with the acute aortitis.

CONCLUSIONS

Previous pathologic changes in a vessel whether atherosclerotic or syphilitic, predispose to acute infection of its wall either through direct implantation on its surface or through the vasa vasorum.

The presence of a concomitant acute inflammation does not influence the histologic picture of a syphilitic aortitis.

The presence of polymorphonuclear leukocytes in a lesion even with definite evidence of syphilitic changes should lead to a careful and thorough search, not only for spirochetes, but also for pyogenic organisms as a possible cause for the acute reaction.

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13. Warthin: Am. Heart **1**:191, 1925.

UNIQUE FEATURES OF HODGKIN'S DISEASE (LYMPHOGRANULOMATOSIS)

WITH REPORT OF THREE UNUSUAL CASES AND A SUMMARY OF TWENTY-FOUR CASES STUDIED AT NECROPSY *

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It is ordinarily a rather simple matter to classify abnormal swellings into inflammatory masses or neoplastic growths, but there is one type of lesion, that of lymphogranulomatosis, or Hodgkin's disease, which has caused, and is still causing, a great amount of confusion, both as to terminology and as to classification It will therefore not seem out of place to present an additional study to the voluminous literature already existing on the subject.

HISTORICAL

Hodgkin,[1] in 1832, described as an entity a group of conditions involving the lymph nodes and at times also the spleen, which he found in a series of seven cases. It is likely, however, that in the absence of proper histologic studies, this group included, besides Hodgkin's disease, cases of tuberculosis of the nodes, malignancies and perhaps syphilis, as was well pointed out by Virchow.[2] Later, in 1845, Virchow [3] excluded the frank leukemias from this group, and from then on there began a more rigid classification to form a well defined clinical and pathologic entity. Wilks,[4] in 1865, gave a comprehensive description of this type of cases and suggested the name of Hodgkin's disease. Cohnheim,[5] in the same year, used the name pseudoleukemia. Four years later, Billroth [6] proposed malignant lymphoma as the designation for this condition, and Fisher,[7] in 1897, described twelve cases under this heading. The clinical course of the disease certainly warrants this

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1. Hodgkin: On Some Morbid Appearances of the Absorbent Glands and Spleen, Med. Chir. Tr. **17**:68, 1832.

2. Virchow: Die krankhaften Geschwülste, Berl. klin. Wchnschr. **29**:289 1892.

3. Virchow: Die krankhaften Geschwülste **2**:728, 1864.

4. Wilks: Cases of a Peculiar Enlargement of the Lymphatic Glands Associated with Disease of the Spleen, Guy's Hosp. Rep. **2**:114, 1856; **11**:56, 1865.

5. Cohnheim: Ein Fall von Pseudoleukämie, Virchows Arch. f. path. Anat. **33**:451, 1895.

6. Billroth: Multiple Lymphome; erfolgreiche Behandlung mit Arsenik, Wien. med. Wchnschr. **44**:1065, 1871.

7. Fisher: Ueber malignes Lymphom., Arch. f. klin. Chir. **55**:467, 1897.

designation (malignant lymphoma), since there is no authentic case on record that has not had a fatal termination, a course which is associated only with a very malignant tumor.

With further studies of this condition there developed a strong tendency to consider the disease an infectious granuloma, and the term lymphogranulomatosis, first used by Gross [8] in 1906, has had wide acceptance, especially in Europe. This term is superseded by lymphadenoma in the English literature, while American authors seem to prefer the name Hodgkin's disease. That it is of an infectious nature has not been universally accepted, as can easily be inferred from MacCallum [9] in the recent edition of his "Textbook on Pathology": "Since we have not definitely recognized an infectious agent, we are not quite sure whether Hodgkin's disease is a tumor or not."

POSTMORTEM STUDIES

Recently I had under observation a patient (case 1) that presented, to quote Osler,[10] "one of the most remarkable syndromes in medicine." The disease ran such an unusual clinical course and presented such a very interesting problem as to baffle many excellent men in the profession in making a correct diagnosis. When the final diagnosis of Hodgkin's disease was established by necropsy, I reviewed the necropsy records in the department of pathology at the University of Minnesota to determine the frequency of the condition as there revealed. The records comprise a series of 7,253 cases during a period of over sixteen years, from Jan. 1, 1910, to March 5, 1926. In this series twenty-four cases of Hodgkin's disease were found. This gives an incidence of 0.32 per cent. During the year 1925 alone, eight cases were encountered, constituting more than one third of the entire series of Hodgkin's disease recorded at the university in the period of sixteen years, giving an incidence of 0.8 per cent in the 1,061 necropsies performed for that year.

Of the twenty-four cases, sixteen occurred in men and eight in women, a ratio of two to one, corresponding to the statistics as given in the literature.[11] The age incidence also corresponds with the reported age groups. Fifty per cent of the patients were in the second and third decades, as shown in table 1.

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8. Gross, S.: Ueber eine bisher nicht beschriebene Hauterkrankung (Lymphogranulomatosis cutis), Beitr. z. path. anat. u. z. allg. Pathol. **39**:405, 1906.

9. MacCallum: A Textbook of Pathology, ed. 3, 1924, p. 1101.

10. Osler and McCrae: The Principles and Practice of Medicine, ed. 9, Philadelphia, Lea & Febiger, 1920, p. 740.

11. Ziegler: Die Hodgkinsche Krankheit, Jena, G. Fisher, 1911. Longcope, T. L., and McAlpin, K. R.: Hodgkin's Disease, Oxford Medicine **4**:2, 1921.

As will be seen, the preponderance of cases is in young adult and middle age. In my series, the youngest was 19 years of age and the oldest 66.

The average duration in my series cannot be given with great definiteness, but the majority of cases ran a course under one and one-half years, the shortest was two months, and the longest nine years. The latter case was that of a woman who gave birth to a healthy infant six years after the development of enlarged cervical nodes, and died when the child was 3 years old.

Symptoms.—A gradual loss of strength was recorded in fourteen cases. One-half of the patients complained of loss in weight, and in three of these it was marked. A distressing cough was noted in nine cases. In practically all of these there was involvement of the peribronchial or mediastinal lymph nodes or of the lung parenchyma itself. In three of these nine cases an associated tuberculosis was present. Severe pain in the abdomen was complained of in six cases, and all of

TABLE 1.—*Cases of Hodgkin's Disease Occurring at the University of Minnesota During Sixteen Years*

Age	Cases
19 to 20	2
21 to 30	5
31 to 40	7
41 to 50	2
51 to 60	6
61 to 66	2

the patients had extensive involvement of the prevertebral and retroperitoneal lymph nodes. Two patients complained of profuse night sweats; in one this was definitely not associated with tuberculosis. Severe backache was present in three cases. In one of them there was extensive infiltration into the lumbar vertebrae. Fever was noted in about 50 per cent of the cases. This was for the most part variable in duration and in intensity; some were intermittent and some remittent. In two of the cases, however, the temperature curves were striking, presenting the typical curves of chronic relapsing fever with periods of pyrexia alternating with periods of complete apyrexia. These correspond to the cases first described by Murchison [12] and later by Pel [13] and Ebstein.[14] One of these cases (case 1) will be given below in detail.

12. Murchison, C.: Case of "Lymphadenoma" of the Lymphatic System, Spleen, Liver, Lungs, Heart, Diaphragm, Dura Mater, etc., Tr. Path. Soc. London **21**:372, 1870.

13. Pel, P. K.: Zur Symptomatologie der sogenannten Pseudoleukämie, Berl. klin. Wchnschr. **22**:3, 1885; Pseudoleukämie oder chronisches Ruckfallsfieber? idem. **24**:644, 1887.

14. Ebstein: Das chronische Ruckfallsfieber eine neue Infektionskrankheit, Berl. klin. Wchnschr. **24**:565, 1887.

Pathologic Observations.—The frequency of the involvement of different groups of lymph nodes is given in table 2.

The frequency of the involvement of the retroperitoneal and prevertebral lymph nodes may explain through pressure on ganglions and nerves the many complaints of pain in the back and abdomen. In one case there was involvement only of the liver, spleen, retroperitoneal nodes and the body of a lumbar vertebra. This comprises a typical case of so-called abdominal Hodgkin's disease. This case is similar to that described by Williamson.[15] In five cases the enlarged mesenteric and retroperitoneal nodes formed easily palpable, large tumor masses in the abdomen. In two women the deep pelvic nodes were enlarged, and in one of these the masses led to a clinical diagnosis of carcinoma of the broad ligament with metastases to the liver. In eight cases the nodes showed also tuberculous lesions, and in five of these there was associated pulmonary involvement.

The bodies of the vertebrae were infiltrated extensively in four cases, in two of which the destruction produced a knuckle deformity suggesting Pott's disease. In one case the cord was infiltrated, producing general paralysis, and in another a tumor mass developed extradurally with pressure on the cord which resulted in complete paralysis of the lower extremities. In one case the patient had sustained a fracture of the femur following a slight fall. Later a large tumor mass developed at the site of the fracture, and examination showed extensive infiltration with Hodgkin's disease into the bone, bone marrow and thigh muscles. The intercostal and abdominal muscles were infiltrated in one case manifesting extensive pulmonary involvement.

TABLE 2.—*Involvement of Various Groups of Lymph Nodes*

Retroperitoneal	17
Cervical	15
Inguinal	14
Axillary	12
Mediastinal	12
Mesenteric	7
Femoral	2

Spleen.—The involvement of the spleen forms one of the most characteristic pictures in the disease, according to Sternberg.[16] In our series there was enlargement above 250 Gm. in thirteen cases, in ten the weight was above 350 Gm., in four cases above 800 Gm., and the largest

15. Williamson, C. S.: Hodgkin's Disease (Abdominal Type), M. Clin. N. Amer. **7**:387, 1923.

16. Sternberg: Die Lymphogranulomatose, Klin. Wchnschr. **4**:529 (March 19) 1925.

was 1,100 Gm. The cut surfaces of the spleen showed grayish-white nodules scattered through the parenchyma (fig. 1). The majority of these were miliary and submiliary nodules, while some were rather large tumor masses. There was infiltration in three of the spleens that were normal or subnormal in size. According to the literature, the spleen rarely remains entirely uninvolved. Areas of focal necrosis (fig. 1) are fairly common in this organ. In one case (case 3) the spleen was found so enlarged on physical examination that it resembled the enormous spleens often encountered in myelogenous leukemia or Banti's disease. Splenic enlargements of this proportion are uncommon in Hodgkin's disease.

Liver.—In my series the liver was enlarged above 1,850 Gm. in over 50 per cent of the cases, the largest weighing 3,000 Gm. (case 1). Nearly all of these showed Hodgkin's disease either microscopically or macroscopically. The infiltrations are characteristic and are present principally in the portal spaces and around the bile ducts. This fact may explain the occasional development of jaundice; in our series it occurred in five cases. It is likely that the peribiliary infiltration produces jaundice more frequently than does pressure of enlarged lymph nodes or tumor masses against the large bile ducts.

Lungs.—In nine cases there were peribronchial nodules principally at the hilus of the lungs, and several of these showed extensive infiltrations into the parenchyma. Not infrequently there were large tumor masses involving the lungs that closely resembled carcinoma. In five cases the lungs showed associated tuberculosis, in four of which it was of the acute miliary type. In one there was a large calcified tuberculous nodule. Altogether in my series eight cases were associated with tuberculosis, and sixteen showed no tuberculous involvement. Schreiner and Mattick [17] found tuberculosis very infrequent in their series of forty-six cases. In only four did they find a definite history of tuberculosis in the families. Extensive hydrothorax was present in ten cases. Ascites was also present in six cases.

Skin.—Four cases showed cutaneous involvement. All of these were associated with itching at some time or other. Frequently the itching was intractible and preceded by several years the definite evidences of the disease. In one case the rash was diagnosed German measles. This rash recurred several times later after the diagnosis of Hodgkin's disease had been established. In one case (case 2) not included in these necropsy studies, the rash was extensive (fig. 2) and recurred many times. Itching occasionally occurred without any cutaneous lesions. The his-

17. Schreiner, B. F., and Mattick, W. L.: Radiation Therapy in Forty-Six Cases of Lymphogranuloma (Hodgkin's Disease), Am. J. Roentgenol. **12**:133, 1924.

tologic study of the skin lesions revealed infiltration with the characteristic elements of the disease in most cases (fig. 3). In case 3 (fig. 4) the histology was not entirely characteristic, in that there were no definite large Dorothy Reed cells present. Three cases showed diffuse pigmentation. This is not infrequently associated with the disease. The discoloration at times suggests Addison's disease. In one of the cases which began as an abdominal Hodgkin's disease before the superficial nodes became involved, such a diagnosis had actually been made.

Blood Studies.—A cachectic type of secondary anemia was present in all of the cases in the last stages of the disease. In a few cases the anemia appeared early. The average hemoglobin was between 30 and 60 per cent. In one case it fell to 19 per cent. In seven of the cases the red count was below 3,500,000 with a range of from 1,800,000 to 4,500,000. There was a leukocytosis above 12,000 in thirteen cases, the highest being 55,000. This is a figure higher than is generally given in the literature. A polymorphonuclear leukocytosis between 85 and 88 per cent was present in only four of the cases, although this condition is believed to be not infrequent. A striking feature in some of the cases was the eosinophilia which in four instances ran between 18 and 44 per cent. In one of these, in which the leukocyte count at one time reached 55,000, the eosinophilia varied between 7 and 44 per cent, a remarkable figure, one of the highest reported in the literature. Ten complete blood studies were made on this case, the majority of counts revealing 25 per cent or over. A leukopenia was present in a small percentage of cases; in our series five showed leukocyte counts below 6,000, in three of these the average was 3,000, in one case (case 3), not studied at necropsy, the leukocyte count dropped to 250, remaining at that level for four successive days previous to the fatal termination. In the more acute cases which are associated with high fever over long periods of time leukopenia apparently is more frequent than in the other types. It is for this reason that occasionally a wrong diagnosis of typhoid or relapsing typhoid fever is made. In general, most observers are of the opinion, contrary to that of Bunting,[18] that there is no characteristic blood picture in this disease. In many of the cases the blood picture remains normal until the very advanced stages, when a definite anemia of the secondary type develops. The only outstanding feature, when present, is eosinophilia, which, with large lymph nodes, helps materially in establishing a diagnosis.

Miscellaneous Involvements.—The suprarenals were infiltrated in one case and both ureters and urinary bladder in another. The bone marrow showed infiltration in one case, the one already mentioned in which a tumor mass developed on the thigh following a fracture. The

18. Bunting: The Blood Picture in Hodgkin's Disease, Bull. Johns Hopkins Hosp. **22**:369, 1911; **25**:173, 1914.

infrequency of bone marrow examination at necropsy may explain the fact that only one instance of bone marrow involvement is reported in this series.

In one case the enlargement of the neck was diagnosed goiter. Microscopic study of the specimen removed at operation showed Hodgkin's disease, and later at the postmortem study there was found an extensive infiltration of Hodgkin's disease into the lungs In one case the pericardium was infiltrated.

In only one case of this series was an involvement of the gastro-intestinal tract reported, and that was a massive infiltration around the rectum and anus. This paucity of gastro-intestinal involvement may be more apparent than real, due to rather superficial examinations of that tract, since in the literature such involvement is reported as not infrequent. There are rare cases in the literature in which there is only gastro-intestinal involvement. One such case is reported by Sternberg [16] in which there were present extensive tumor masses in the stomach only. Sternberg cites cases from the literature to show that practically every tissue and organ in the body may become involved.

Biopsy.—Diagnosis was established by biopsy in fifteen cases. In eleven cases the diagnosis was definitely established after the first examination. One case was at first diagnosed as probable tuberculosis, but of a peculiar type. In another case both Hodgkin's disease and tuberculosis were found. No definite diagnosis was given at the first biopsy in one of the cases, but Hodgkin's disease and tuberculosis were ruled out. The second biopsy showed the definite lesions of Hodgkin's disease.

One of the cases reported above is an interesting example of the confusion in terminology. This case was recently diagnosed through biopsy, one year after the onset of the disease and six months before death, by a leading clinic in the country as lymphosarcoma of the Hodgkin's type. This diagnosis was made in spite of the fact that the clinical course of this case was typical of Hodgkin's disease. At necropsy there was found a generalized Hodgkin's disease of the lymph nodes and organs including the liver, spleen, lungs and vertebrae which histologically showed Hodgkin's disease in the advanced stages of fibrosis. It is curious that prominent American physicians should continue to confuse the terminology of Hodgkin's disease and lymphosarcoma. Such a loose and unscientific use of terms leads to erroneous diagnoses. European clinicians have abandoned this vague terminology and rightfully consider Hodgkin's disease as a well-defined clinical entity. When a biopsy suggests Hodgkin's disease in any way because of the presence of characteristic cells, a tumor diagnosis should be precluded.

There is one type of lesion in which confusion is likely to occur, that of Hodgkin's sarcoma, cited by Ewing [19] as being rare. In this lesion

19. Ewing, James: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1915, p. 334.

sarcoma is engrafted on the inflammatory tissue of Hodgkin's disease and is not an integral part of the disease.

Occasionally a single biopsy may be misleading, since at times the pathognomonic features may not be present. An instance of this is well illustrated in case 1.

Treatment.—In five cases of the series roentgen-ray treatment was used. There was practically no change brought about in the progressive course of the disease. The masses treated would disappear, but new ones would arise apparently unhindered. Klewitz and Lullies [20] treated sixteen patients with the roentgen ray. The average duration after the onset was twenty months. Only one patient survived six years. They concluded that the treatment does not prolong life. Schreiner and Mattick [17] report a series of forty-six patients treated at the New York Institute for the Study of Malignant Disease. They find that the adenopathies disappear and the patients are made more comfortable under roentgen-ray or radium treatment, but the course of the disease apparently remains unaffected. Sternberg,[16] however, believes that life is prolonged through roentgen-ray therapy, and cites one of his patients as living for ten years. Still, he says emphatically that practically every case ends fatally within a few years, regardless of the type of treatment used. The disease relentlessly progresses through an ever increasing anemia and cachexia to death. Byfield [21] seems to agree with Sternberg that longer remissions may be obtained through this procedure.

Personally, I am not convinced that life is prolonged by roentgenotherapy, unless it be through the dissolving of masses that produce pressure phenomena because of location, as for example, mediastinal masses pressing on trachea, lungs or heart. Only in such instances does it seem to me that the apparent improvement actually prolongs life. In all other instances the patient dies with small, and at times invisible, masses instead of large ones. Minot [22] reaches the same conclusion relative to roentgen-ray therapy in cases of chronic myelogenous leukemia. "Irradiation has had little effect on prolonging the life of these patients."

REPORT OF CASES

CASE 1.—*History.*—Mr. J. D., aged 42, was admitted to St. Mary's Hospital, Jan. 5, 1926, complaining of recurrent attacks of high fever. He was a farmer, born and raised in Minnesota, and had been well until 1910, when he was operated on for acute appendicitis, but perforated gastric ulcer was found. Following this he had some gastric distress. One year later he was operated on at Rochester,

20. Klewitz, F., and Lullies, G.: Beitrage zur Prognose des malignen Granuloms, Klin. Wchnschr. **3**:276, 1924.

21. Byfield: Hodgkin's Disease, in Tice: Practice of Medicine, Hagerstown, Md., W. F. Prior Company, Inc. **5**:144, 1921.

22. Minot, G. R.; Buckman, T. E., and Isaacs, R.: Chronic Myelogenous Leukemia, J. A. M. A. **82**:1489 (May 10) 1924.

when a gastro-enterostomy was performed. At this time he had noticed small nodules in his neck about the size of navy beans or peas, which he was told were of no importance. Following this operation he was well until 1921, when lumps appeared on both sides of the neck, more marked on the left side. These were painless, and not tender, and gradually increased to a mass about the size of a small orange, which protruded from the side of the neck. The enlargement developed during the course of one year. He consulted a physician and was given an ointment, after which the mass gradually subsided until it disappeared entirely, and did not recur.

About the middle of April, 1925, on a Saturday afternoon, he contracted what was thought to be a cold, with a sore throat and plugged nose, some aching of the limbs and a weak, tired feeling. The attack began with a slight chill, was accompanied by a temperature of 104 F. for several days and then subsided.

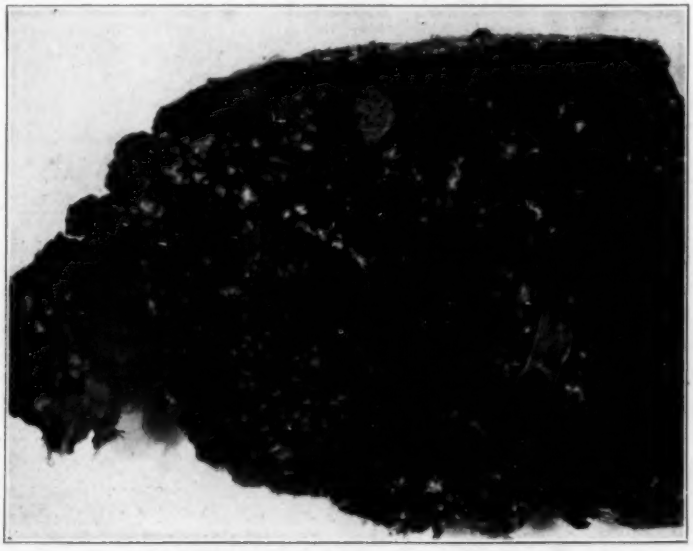

Fig 1 (case 1).—Cut surface of portion of spleen. Note the numerous miliary and submiliary nodules of "lymphogranulomatous" tissue. The larger areas are areas of necrosis.

Exactly three weeks from the onset of this attack on a Saturday he again experienced a feeling of malaise, loss of appetite, slight headache and fever, which rose rapidly, reaching 105 F. on the second or third day and continuing with slight remissions for about a week, when it slowly dropped to normal. From then on he had recurrences of these attacks every three weeks, with not more than one day's variation in the time of onset, and during the first few days of high fever he would feel so well that he attended to his usual chores, such, for instance, as milking the cows. It was very difficult for his wife (who had been a nurse) to keep him in bed. He would regain his usual strength, though at times he would lack energy. Each succeeding attack seemed to be a little more severe than the previous one. A general average of 104 F. was reached each time. He was admitted to the hospital on the tenth day of the twelfth attack with a temperature of 103 F. (fig. 12).

Examination.—The patient appeared comfortable in bed. The face was flushed, with a marked "butterfly" injection of the venules over the nose and cheeks. There was a purple cyanosis of the ears and back of the neck; the tongue was moist and slightly coated; mild pyorrhea, gingivitis and caries were present, also some injection of the pharynx. The eyes were normal. The patient said that he had had diplopia six weeks and three weeks before. Except for a few rhonchi throughout the chest, the lungs were normal. There were slightly enlarged lymph nodes on both sides of the neck, in the supraclavicular and posterior triangles, more marked on the left; these were discrete and ranged from the size of a pea to that of a lima bean, and were firm and freely movable. The heart was normal. There were three large scars from previous operations over the abdomen, no tenderness, and no masses palpable. The liver and spleen were not palpable; axillary, inguinal and other superficial nodes were not palpable. The temperature was 103 F., the pulse rate 120, the blood pressure 96 systolic and 58 diastolic. The extremities were normal; neurologic examination gave negative results.

From the history of a chronic relapsing type of fever and the presence of enlarged nodes on both sides of the neck, together with the previous history of masses in the neck, a diagnosis of Hodgkin's disease with Pel-Ebstein type of fever was made. Two days later, a biopsy was performed on three of the cervical nodes, which showed grossly extensive caseation necrosis, suggesting tuberculosis. Microscopically, the sections showed a peculiar homogeneous necrotic material surrounded by a thin wall of connective tissue containing a few lymphocytes (fig. 5). The usual tuberculous reaction around the necrotic area was absent in all sections studied. Because of the extensive necrosis, an eminent pathologist ruled out Hodgkin's disease. He said that the type of necrosis was different from a tuberculous involvement and that the lesion was one which he could not exactly identify. Later he ventured the opinion that it was probably an atypical tuberculosis.

Stereoscopic plates of the chest showed a calcified nodule about 2 cm. in diameter in the middle of the left lung, probably a healed Ghons tubercle. The roentgen-ray diagnosis was probably an old healed tuberculous involvement.

Blood examination showed on admission a hemoglobin of 85 per cent, red count 5,300,000, leukocytes 4,800 and a fairly normal differential count. Repeated blood studies showed a leukocyte count ranging between 2,800 and 4,900, the hemoglobin three days before death being 70 per cent. Repeated blood cultures were negative with the exception of one, which after standing for a period of ten days showed *Streptococcus viridans.* The stools were negative for parasites, ova and occult blood. The Widal reaction was negative. Roentgen-ray examination of the nasal accessory sinuses showed no pathologic condition present. Repeated urinalyses were negative up to about one week before death, when a double plus albumin and four plus granular casts appeared. At the same time urobilinogen appeared, and later large amounts of bilirubin. The Wassermann test was negative. Blood smears showed a secondary type of anemia. Repeated search revealed no malarial parasites or *Spirochetae obermeieri.*

Clinical Notes.—Jan. 9, 1926: Occasional coarse crackling râles were present over both bases. The patient felt comfortable.

January 10: The patient felt quite well. He had a peculiar lemon yellow tinge to the face, most marked around the eyes and below the cheek bones. The pulse rate was 106, bounding; the chest was normal.

January 12: The blood pressure was 120 systolic and 58 diastolic.

January 13: The patient was up and around; he felt quite well and had no pain or aches.

January 16: He felt very well. He was gaining in strength and weight, and his appetite was good. The temperature was normal. An attack was to begin in the afternoon or the next day.

January 17: The patient did not look so well; his pulse was rapid, 136; the temperature was 102.5 F. The temperature started climbing in the afternoon of the previous day, when it reached 100 F., and it was rising steadily.

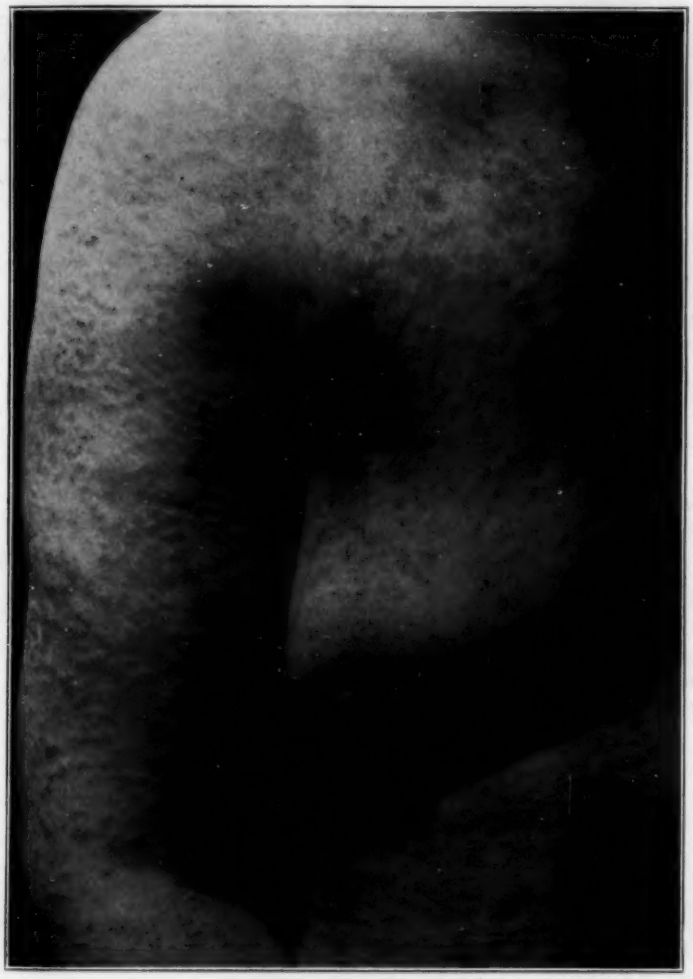

Fig. 2 (case 2).—The definite infiltrated papular rash is well shown. This rash was diffusely scattered over the entire body. Figure 4 is from a section of one of these nodules.

January 18: The temperature was 105.2 F. The patient said that he felt fine, with no pains and no aches. He only felt a little tired and saw no reason for being confined to bed. His pulse rate was 150, full and bounding, and often dicrotic; the respiration was 24. Physical examination gave negative results.

January 19: Respiration was 34, the pulse rate 150, blood pressure 124 systolic and 44 diastolic; the cervical nodes were a little larger, the spleen palpable, the margin firm; the liver palpable, being 1 cm. below the costal margin on deep inspiration. There was no discomfort other than weakness.

January 20: The patient felt uncomfortable after a bad night; the temperature was 104 to 105.2 F., with very little response to sponging. There was some delirium. He had definite tremors of the lips and hands. The chest was clear. The liver was 4 cm. below the costal margin; the spleen 3 cm. below the margin.

January 23: The patient was getting weaker, with a definite icteric tinge to the sclera and skin; the tongue was furred; respiration 35; the skin was moist; the pulse rate was 120, full and bounding; the heart and lungs were normal; the abdomen was distended and somewhat tense. Frequent attacks of hiccoughing occurred during the last forty-eight hours. He had not voided for eighteen hours; only 150 cc. of very dark colored urine were removed by catheter.

January 24: The patient was comatose and somewhat delirious. There was coarse twitching of the eyelids and hands and marked icterus of the entire body. The pulse rate was 130, respiration 32. There were a few moist râles at the bases of both lungs posteriorly. The liver was 5 cm. below the costal margin. The tongue was dry and glazed.

January 25: The patient looked very toxic. He had muttering delirium with picking of the bedclothes, marked coarse twitching of the muscles of the face, hands and arms. He had an anxious expression. Jaundice was marked. The pulse was of fairly good quality, but less bounding. There was moderate cyanosis of the finger-nails.

January 26: The patient died at 1 p. m.

Necropsy.—This was performed three hours after death by Dr. E. T. Bell of the department of pathology, University of Minnesota.

Necropsy revealed: a well developed and well nourished body; three plus jaundice; no edema; enlarged lymph nodes in the left posterior triangle of the neck; no free fluid in the abdomen; the weight of heart, 325 Gm.; blood not coagulated, but thin and watery; congestion of the dependent parts; calcified nodule 1.5 cm. in diameter in middle of upper lobe of left lung; weight of spleen, 900 Gm., firm, surface mottled with whitish areas, miliary nodules scattered through the cut surface suggesting miliary tuberculosis (fig. 1); small accessory spleen presenting the same structure; liver large, 3,000 Gm., cut surface showing numerous minute, whitish areas in portal spaces; no disease of gallbladder or bile passages; gastro-intestinal tract, pancreas and suprarenals normal; kidneys each weighing 300 Gm., cortices cloudy and swollen; preaortic lymph nodes markedly enlarged, both thoracic and abdominal. On section they showed large caseous areas; a few similar nodes were present in the mediastinum.

Microscopic examination of the spleen, liver and lymph nodes showed typical Hodgkin's disease with numerous characteristic Dorothy Reed cells.

Postmortem diagnoses were: (1) Hodgkin's disease, involving spleen, liver, preaortic and mediastinal lymph nodes; (2) Ghon tubercle; (3) acute toxic nephrosis (cloudy swelling).

Comment.—The histologic pathology of this case is in every way typical of Hodgkin's disease and corresponds exactly to the description

of Sternberg [23] and Reed.[24] As described by them, the beginning process consists of a proliferation of the lymphoid cells. An examination of a gland at this stage presents the picture of a simple hyperplasia and diagnosis is therefore difficult. Later there is a proliferation of the reticulo-endothelial cells, and these gradually replace the normal tissue of the gland. Between these cells there are present in greater or lesser numbers large cells with characteristic nuclei that are variously lobed or multinucleated (fig. 6). The importance of this type of giant cell as characteristic of the disease was emphasized by Reed, and they have since been known in the American literature as the Dorothy Reed cells.

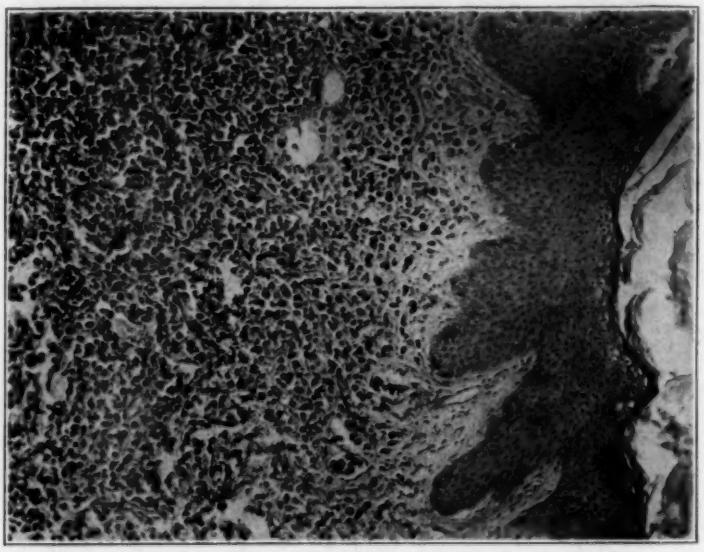

Fig. 3.—A section of skin from one of the necropsy cases discussed in the text. The characteristic Hodgkin's granulation tissue is well shown. Some of the lymph spaces are filled with large endothelioid cells. (Cf. fig. 14.)

As the disease progresses, scar tissue forms until dense fibrous connective tissue replaces the cellular elements (fig. 7). In addition to the foregoing, eosinophil leukocytes may be abundant, and these, when present, complete the characteristic picture. Their presence in the lymph nodes is probably coincident with an eosinophilia in the blood stream at some time or other and occurs perhaps in from 20 to 25 per cent of the cases.

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23. Sternberg: Ueber eine eigenartige unter dem Bilde der Pseudoleukämie verlaufende Tuberkulose des Lymphatschen Apparates, Ztschr. f. Heilk. **19**:21, 1898.

24. Reed, D.: The Pathological Changes in Hodgkin's Disease, Johns Hopkins Hosp. Rep. **10**:133, 1902.

The picture described above is identical in whatever tissue or organ it may be found, be it spleen (fig. 8), liver (fig. 9), lymph nodes (fig. 10) or skin (fig. 3), and is absolutely pathognomonic of the disease.

When the large proliferating reticulo-endothelial cells and the giant cells become dense and numerous, the microscopic picture may suggest sarcoma. Careful study, however, will reveal the fact that the tissue is not made up of this one type of cell alone, but that other types are present and closely associated, which rules out a diagnosis of sarcoma.

I wish to call attention to the extensive necrosis present in the lymph nodes in case 1. Large areas of caseation necrosis are generally considered characteristic of tuberculosis, and their presence is taken to be definitely indicative of that disease as against Hodgkin's disease. I hold this to be an error. Though extensive areas of necrosis completely involving many nodes were present in case 1, a careful search revealed no evidence of tuberculosis. There were no tubercles, no accumulation of lymphocytes or epithelioid cells, no giant cells of the Langhans type, no inflammatory tissue in any way suggestive of a tuberculous lesion, and yet there was extensive necrosis. This necrosis was a definite Hodgkin's necrosis.

The biopsy in case 1 not only did not help in establishing a diagnosis, but actually led away from the clinical diagnosis of Hodgkin's disease already tentatively made. Careful studies of the nodes postmortem, especially of the prevertebral group, revealed that all the remnants not yet necrotic presented a picture of Hodgkin's disease and not of tuberculosis (fig. 10). I believe that errors in diagnosis of Hodgkin's disease are not infrequently made microscopically as well as grossly because of the general opinion that massive caseation necrosis is indicative of tuberculosis.

CASE 2.—*History.*—Mrs. H. C., aged 56, was first seen on Sept. 14, 1922, complaining of pain in the precordium and edema of the legs. The family and past history were negative. The patient had always been well up until the present illness. A hysterectomy had been performed when she was 44; menopause had been present since then. The patient was well until the spring of 1919, when she developed small lumps in the back of the neck and then a large mass below the angle of the right side of the jaw. This increased to the size of an orange, when it was treated with radium, after which it gradually disappeared. The following year she was entirely well. In April, 1920, she developed a rash like measles, which was associated with fever, and was confined to bed for three weeks. In July, 1921, she again developed a fever. At this time she was told that the urine was bad. In the fall of 1921, she began to feel tired; her mouth was dry; she was very thirsty, drank large quantities of water and urinated frequently. In April, 1922, she fell down and bruised herself, and was confined to bed for thirteen weeks. She was treated for heart disease and diabetes at the same time. At that time she again developed a pink rash over the body composed of discrete papules from 3 to 10 mm. in diameter. These were definitely raised and indurated.

Examination.—On examination in September, 1922, the patient was found to be well nourished, with a pulse rate of 72, a blood pressure of 162 systolic and 70 diastolic, and an extensive papular rash over the whole body (fig. 2)—front, back, abdomen, arms, forearms and thighs. The tonsils were large; there was gingivitis of the lower teeth, with a plate for the upper. There were large lymph nodes in the posterior and supraclavicular triangles of the neck, the largest measuring 2 cm. in diameter. The right maxillary and right axillary nodes were the size of walnuts, the right inguinal nodes the size of hen's eggs, and the left inguinal nodes the size of hazelnuts. All nodes were discrete and freely movable. Cardiac dulness was increased both to the right and to the left, with increased mediastinal

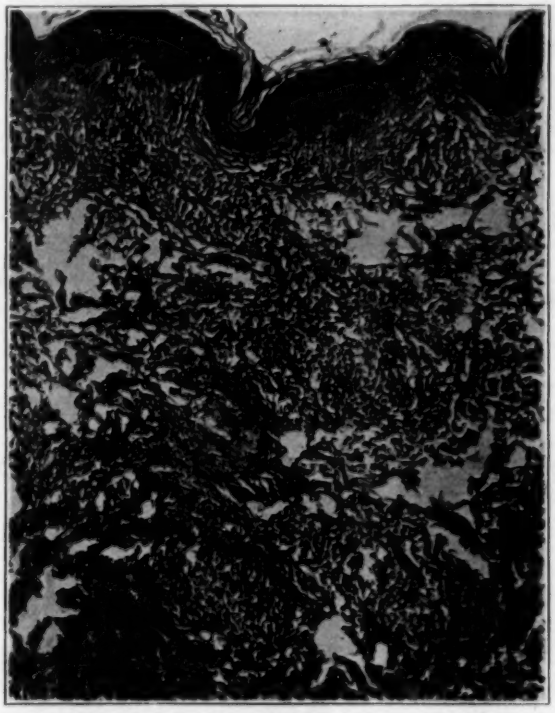

Fig. 4.—Section from skin in case 2. The large reticular type of cell is not so evident as in figure 3.

dulness; there was a soft systolic murmur at the apex transmitted to the axilla. The chest showed poor expansion with lagging on the left side. The spleen and liver were not palpable. The biceps, triceps and knee reflexes were exaggerated.

The first examination of the urine showed sugar +++; subsequently it was normal. Blood examination on September 14 revealed a hemoglobin of 86 per cent, red blood count 5,200,000, leukocytes 5,800, with a differential count of polymorphonuclears 64 per cent, lymphocytes 23 per cent, large mononuclears 5 per cent, transitionals 3 per cent and eosinophils 4 per cent. On December 11 the hemoglobin was 54 per cent, the white count 3,400, with eosinophils 7 per cent. On March 24, 1923, the hemoglobin was 34 per cent., the red count 1,900,000, the white count 1,800 and a few normoblasts.

Clinical Notes.—Dec. 11, 1922: The condition was better; the skin rash had disappeared.

December 26: The patient felt very weak; the spleen was markedly enlarged, 10 cm. below the costal margin; the liver, to the level of the umbilicus.

Jan. 2, 1923: The patient felt weak; her appetite was poor; the spleen and liver were very large; the skin rash reappeared with a papular eruption from 1 mm. to 1 cm. in diameter.

March 1: The patient entered St. Mary's Hospital. Her temperature was 102 F.; it was irregular for about ten days, ranging between 97 and 101 F., then to normal from then on; the pulse rate varied from 110 to 130; respiration, from 20 to 40. Physical examination showed very large superficial lymph nodes, the liver receded to 1 cm. below the costal margin and the spleen to 3 cm. below the costal margin. The patient showed marked dyspnea, accompanied by deep cyanosis of the finger-nails and lips. The lower half of the right part of the chest was fixed, the breath sounds absent.

March 13: The patient was much worse. The right side of the chest was full of fluid, and generalized edema was developing.

March 14: One thousand cubic centimeters of clear amber fluid was aspirated from the right side of the chest; breathing was a little easier.

March 19: There were signs of fluid reaccumulating. Severe dyspnea was present.

March 20: Fifteen hundred cubic centimeters of similar fluid was aspirated.

March 22: The patient was much worse. Anemia was profound. There was a purpuric rash over the right arm, the right shoulder and the back. Urine showed one plus albumin, one plus hyaline and three plus granular casts.

The patient died on March 25, 1923.

Biopsy of the skin showed infiltration into the corium with small lymphocytes (fig. 4) and a few large reticular cells, but no characteristic Dorothy Reed cells. Biopsy of a cervical node showed extensive hyperplasia of lymphoid tissue with areas of fibrosis and a few eosinophils. The diagnosis was Hodgkin's disease.

The patient had been given six roentgen-ray treatments with some reduction in the size of the nodes, but there was no clinical relief. Necropsy was not performed.

Case 3.—*History.*—Mr. D. W., aged 44, first seen on Dec. 2, 1924, complaining of cramps in both legs of several years' duration, painful joints, especially the knee and ankle joints, of ten days' duration, a purplish purpuric rash on the legs of one week's duration, a large mass in the right axilla, hoarseness, progressive loss of weight and increase in weakness. His wife and two children were well. His past history was negative; his habits were regular.

His present trouble started in February, 1924, with hoarseness and severe headaches. Two months later, he noticed a mass in the right axilla about the size of a hen's egg, which gradually increased in size. It was diagnosed lipoma. During the summer of 1924, he noticed that he was unusually sensitive to mosquito bites. He would develop first a swelling, with considerable inflammation, which later would ulcerate and become encrusted. These healed very slowly, a few around the ankles remaining encrusted and unhealed up to the time of his examination. For thirty years he had occasionally had nosebleed. Two weeks previous, he developed pains in both legs, first in the knees and later in the ankles. This prevented him from walking up stairs. One week later a purplish rash appeared, the spots coming out in crops.

Examination.—Examination at this time revealed a well developed, well nourished man with a pulse rate of 70, a blood pressure of 120 systolic and 74 diastolic. Both legs were peppered with petechial spots extending up the thighs. Both tonsils

were extremely large, the size of a large hen's egg; these were apparently not inflamed but simply hypertrophied. The patient said that he first noticed his tonsils enlarging about six months before. The cervical, axillary, femoral, inguinal and epitrochlear nodes were markedly enlarged. The mass in the right axilla was the size of a large grapefruit; on careful palpation it was found to consist of a number of very large discrete lymph nodes. Many of the superficial nodes were enlarged to the size of walnuts. The liver edge was not palpable, but on percussion seemed to extend several centimeters below the costal margin. The spleen was enormous, extending 10 cm. below the costal margin in the midclavicular line and 1 cm. to the right of the midline, the lower edge being below the umbilicus.

Because of the very large spleen, the peculiar skin reaction to mosquito bites (poor healing power), the massive tonsils, the painful joints and the purpuric rash, a tentative diagnosis was made, (1) of leukemia and (2) of Hodgkin's

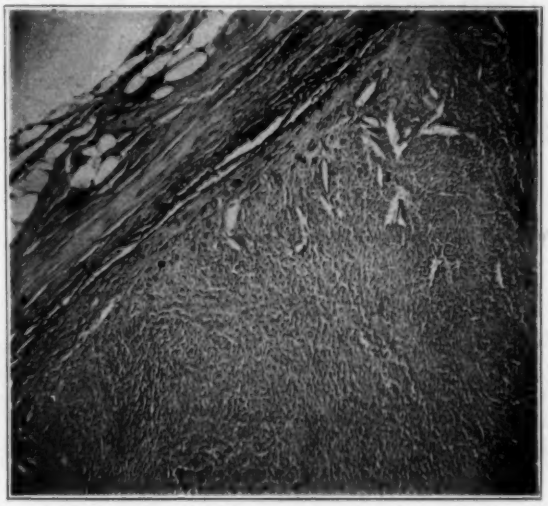

Fig. 5 (case 1).—Section of cervical lymph node removed at biopsy. The outer edge shows a few fat cells, then a layer of dense hyaline connective tissue on the inner edge of which are occasional lymphocytes. The rest of the section shows caseation necrosis with occasional cholesterin crystal spaces. The complete absence of tuberculous granulation tissue is evident. Although caseation necrosis is not infrequent in Hodgkin's disease, calcification is rare.

disease. The blood study speedily ruled out leukemia. It remained necessary to perform a biopsy to establish the diagnosis, but especially to rule out aleukemic lymphadenosis or myelosis. Supraclavicular glands were excised on December 9, and a study of the pathologic condition revealed a typical case of Hodgkin's disease.

Blood examination on December 3 showed: hemoglobin, 62 per cent; red blood count, 4,600,000; white count, 11,500, with a differential count about normal. The vital capacity was 4,800. Urinalysis was negative. Bleeding and clotting time were normal. Roentgen-ray examinations of the chest were negative. The patient was given roentgen-ray therapy, twenty-six exposures in all, the first on January 7 and the last on Aug. 21, 1925. These exposures were given over the different

areas of the enlarged lymph nodes and also over the spleen and tonsils. From the beginning of the treatment the patient showed gradual improvement, the masses decreasing progressively in size.

Clinical Notes.—Jan. 12, 1925: The patient had a severe reaction following roentgen-ray treatment.

January 27: The cervical nodes were definitely smaller, as were the tonsils smaller.

February 2: He feels much better than at any time during the previous two months. All lymph nodes had decreased in size.

February 9: There was a mass in the right axilla the size of a large hen's egg.

March 11: Many of the nodes were reduced so that they were barely palpable. The spleen was only slightly reduced; the tonsils were about one third of the previous size; the edema and rash of the legs had disappeared.

May 1: The patient said that he was in good health and strong. The hoarseness had disappeared. The tonsils were only slightly larger than the average normal.

June 8: He had a severe reaction to a mosquito bite on the preceding day similar to that of the previous year; a large tense vesicle the size of a marble developed, containing clear fluid. Most of the nodes were just barely palpable. The spleen was reduced to 1 cm. below the costal margin.

July 28: All nodes were barely palpable. There was a mass in the right axilla the size of a walnut. The spleen was 4 cm. below the margin; the liver was palpable.

August 17: The patient was feeling very well, better than for several years. He played golf for the first time in four years.

August 30: He did not feel well; he thought that he had taken cold; he had a severe nosebleed at 7 p. m. Ordinary means did not control it.

August 31: He was given several injections of fibrinogen; his nose was packed as the bleeding was continuous.

September 1: At 11 a. m., the posterior and anterior nares were packed; the oozing continued. At 7:30 p. m., he was very uncomfortable. The temperature was 104.2 F. He was taken to St. Mary's Hospital and fibrinogen injected.

September 2: A transfusion of 500 cc. of blood was performed; before transfusion the hemoglobin was 22 per cent, the red blood count 1,900,000, the leukocyte count 350; there was some polychromatophilia and a few normoblasts.

September 3: The blood picture was unchanged. The leukocyte count was 250. The patient was irrational at times. The pulse rate was 100 systolic and 102 diastolic. The temperature was 103 to 104 F.

September 4: He had a severe chill, lasting one-half hour. The temperature rose to 107.4 F., axillary. The patient was stuporous. He died at 2 p. m. Necropsy was not performed.

COMMENT

Each of the three cases reported in detail has some unique features, but of these case 1 is without question the most interesting. The striking feature was the history of severe attacks of a chronic relapsing type of fever recurring with unusual regularity at three week intervals. The periods of pyrexia varied from six to twelve days, the majority of the attacks lasting from seven to nine days. During the periods of apyrexia the patient apparently felt well and normal. The regularity with which

the attacks of fever recurred strongly suggests an infection with a parasite similar to the *Plasmodium malariae* except that in this case the cycle was three weeks instead of one, two or three days (quotidian, tertian, quartan). The physical examination was negative, and gave no basis for diagnosis. Had there been lymphadenopathy of the superficial glands, a definite diagnosis of Hodgkin's disease with Pel-Ebstein type of fever would have been made. However, even in the absence of enlarged superficial nodes or enlarged spleen, such a diagnosis tentatively suggested itself as the one most likely. No other condition could be thought of which could present twelve regular successive exacerbations

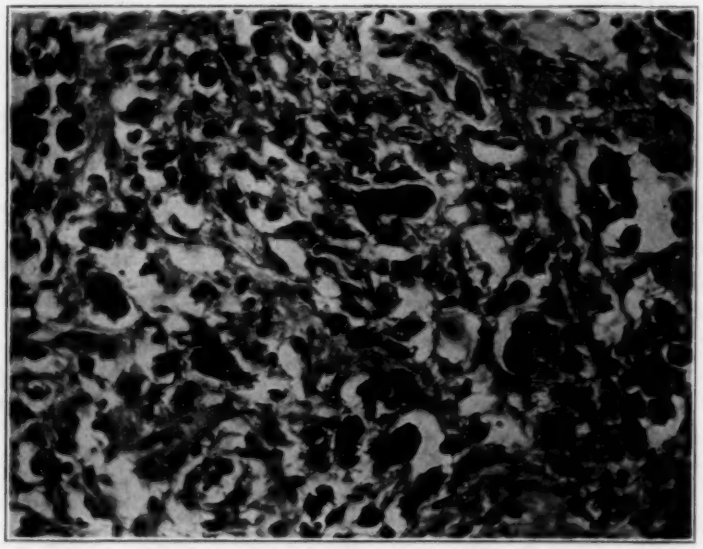

Fig. 6.—Section from lymph node showing typical picture of lymphogranulomatous tissue. The large Dorothy Reed cells and proliferated reticulo-endothelial cells are well shown.

and remissions of fever. The confidence in the tentative diagnosis was somewhat shaken when the biopsy of the cervical lymph nodes showed extensive necrosis, for I then held the current belief that extensive necrosis militates against Hodgkin's disease and is indicative of tuberculosis. A knowledge of the occurrence of extensive necrosis of this type with Hodgkin's disease would have given more confidence in the original diagnosis.

Few cases of this type of Hodgkin's disease with chronic relapsing fever have been reported in the literature. MacNalty,[25] in 1911,

25. MacNalty: Lymphadenoma with Relapsing Pyrexia, Quart. J. Med. **5**:58, 1911.

reviewed the literature carefully, and in his excellent article on "Lymphadenoma with Relapsing Fever" he cites thirty-two cases, five of his own and twenty-seven collected from the literature. Of these, two of his own and six from the literature correspond to case 1 reported here, in that there was no enlargement of the superficial or mediastinal nodes. Whittington,[26] in 1916, added another similar case. Longcope [27] cited a case in which the relapsing fever continued over a period of five years. He, together with other observers, believes that the rise in temperature is due to a secondary infection of some kind. In my opinion, such an assumption is untenable. For it is difficult to see how any of the ordinary types of bacteria producing secondary infections could induce recurring attacks of fever with such precise regularity as obtained in case 1. It is equally inconceivable that reinfections could occur with such remarkable regularity.

The first case of this type mentioned in the literature was reported in 1870 by Murchison,[12] who described periodic outbursts of fever with enlarged glands in a child 6 years old, these persisting during a period of two and one-half years. The most careful discussion of this type of case was made by Pel [13] in 1885 and 1887, and by Ebstein [14] in 1887. Pel's first patient was a man, aged 25, who ran four periods of pyrexia during a four months' course of illness. The febrile periods were from ten to thirty-two days and the afebrile from eight to fifteen days. He reported this case under the title "The Symptomatology of So-Called Pseudoleukemia." Two years later, he reported two more cases under the title of "Pseudoleukemia or Chronic Relapsing Fever?" in which he takes Ebstein to task for considering this condition a "chronic relapsing fever, a new infectious disease" (fig. 13). Figure 11 is taken from Pel's case 3, which corresponds closely with the temperature curve of case 1 in my series (fig. 12). Ebstein made a valuable contribution to the subject of Hodgkin's disease associated with chronic relapsing fever in his detailed and accurate description of a then unknown condition. He insisted that this type of disease must be differentiated from pseudoleukemia and the ordinary types of relapsing fever (i. e., due to *Spirochaeta obermeieri, duttoni,* etc.), and that these cases present a definite clinical entity. He was correct in every detail except that he did not definitely associate this type of case with the whole clinical group now designated by the name of Hodgkin's disease.

Case 2 presents a typical clinical case of Hodgkin's disease extending over a period of four years. The interesting feature of this case is the skin lesion. When the rash first appeared associated with fever it was

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26. Whittington: Acute Hodgkin's Disease with Involvement of the Internal Glands and Relapsing Pyrexia, Quart. J. Med. **9**:83, 1916.

27. Longcope, T. L., and McAlpin, K. R.: Hodgkin's Disease, Oxford Med. **4**:2, 1921.

naturally diagnosed measles. Later the rash reappeared, but in a more papular type of lesion in which the papules averaged about 2 mm. in height. The specific cutaneous lesions associated with Hodgkin's disease generally present the characteristic histologic structure found in other organs (fig. 3.). In this case the histologic structure was somewhat atypical by the absence of the large reticulo-endothelial cells (fig. 4). Gross [8] was the first to describe and identify this type of lesion.

Shelmire [28] gives an excellent summary of Hodgkin's disease of the skin. He discusses in detail two types, the toxic nonspecific eruptions and the true lymphogranulomatous lesions. He calls attention to the fact that pruritus is a manifestation of disease of the lymphatic glands and

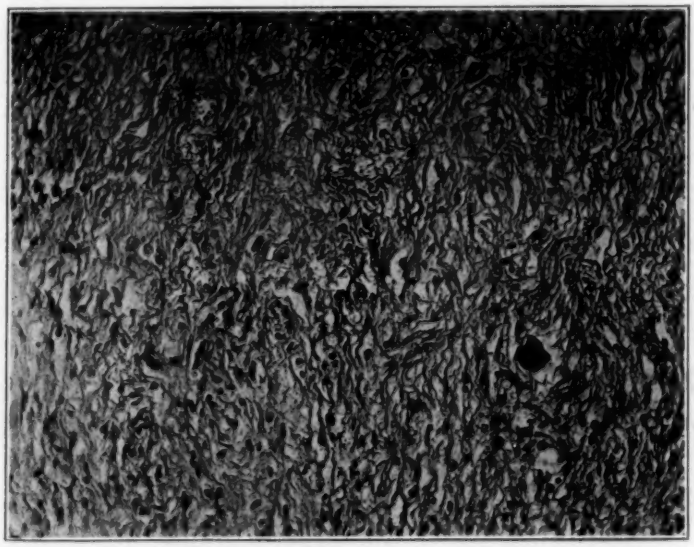

Fig. 7.—Section from lymph node in late stage of Hodgkin's disease. The collagenous fibrils have entirely replaced the lymphoid tissue. A single remaining giant cell is well shown in the section.

is probably the result of an autointoxication from the absorption of irritating toxins produced in the diseased glands. He reports three cases, one of which had been diagnosed and treated as scabies, and another as acne.

Ziegler [11] states that skin lesions occur in about 25 per cent of the cases. This is probably higher than is the experience of most observers. Pruritus is probably the commonest cutaneous manifestation and is reported to occur in from 10 to 15 per cent of the cases. In my small series this condition occurred in about 20 per cent.

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28. Shelmire, Bedford: Hodgkin's Disease of the Skin, South. M. J. **18**:511 (July) 1925.

Case 3 is interesting because of several rather unusual features. The most striking perhaps is the very large spleen. It is unfortunate that the case could not be studied at necropsy, but from the size of the spleen elicited clinically, the organ must have weighed between 1,800 and 2,000 Gm. Such a splenomegaly is more frequently associated with myelogenous leukemia or Banti's disease, since Hodgkin's disease generally gives only a moderate enlargement of the spleen. A number of other observations in this case also suggested leukemia rather than Hodgkin's disease. The purpuric rash especially early in the disease, the painful joints, the peculiar skin reaction to injury, the massive tonsils, all these together with the very large spleen are conditions more commonly

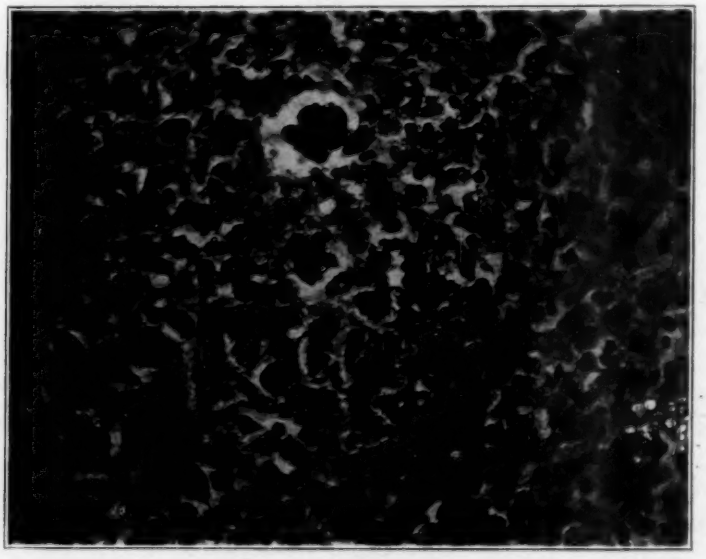

Fig. 8 (case 1).—Section of spleen. Besides the large reticulo-endothelial cells a group of six large cells undergoing mitosis are well shown in a clear lymph space.

encountered in leukemia than in Hodgkin's disease. It was therefore surprising that the blood picture was entirely normal.

The course of the disease in this case is worth while noting. The improvement following roentgen-ray therapy was striking clinically as well as anatomically; the massive lymph nodes, the tonsils and even the spleen receded under its treatment. It is the general experience that the spleen reduces in size much more slowly than the lymph nodes. That was the experience in this case. However, it finally shrank from a mass which filled a great part of the abdomen to one that was barely palpable below the costal margin. But just when the improvement was most marked and the patient was feeling at his best, he suddenly developed an

exacerbation of the disease which manifested itself in a slight enlargement of the spleen, a profound anemia, a high fever and an uncontrollable epistaxis. The anemia presented a picture characteristic of the aplastic pernicious type. The leukopenia was the most marked that I have ever observed clinically or seen reported in the literature. The possibility of overexposure to the roentgen ray cannot be entirely eliminated, but it is well known that untreated cases of Hodgkin's disease often present similar courses in the late stages. In this case, as in so many others, is illustrated the hopelessness of the disease as far as therapy is concerned. Exposures to roentgen ray or radium temporarily improve the patient clinically only. The downward progressive course of the disease continues unchecked.

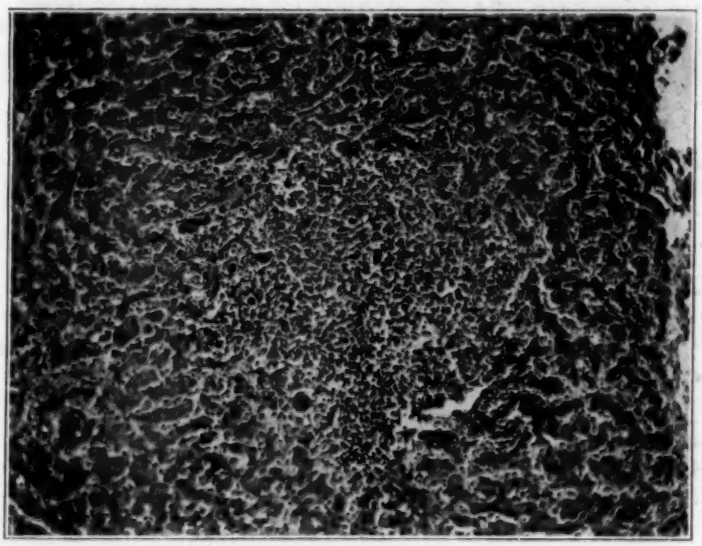

Fig. 9.—Section of liver showing typical Hodgkin's nodule. The tissue is identical with that in the lymph node in figure 10.

ETIOLOGY

One of the most interesting phases of this problem is the question of the etiology of this disease. That this is an infectious disease, as was pointed out by Ebstein,[14] has been generally, although not universally, accepted. Case 1 presents a clinical course with pyrexia that has practically no counterpart in neoplastic diseases, although a few rare cases of sarcoma with relapsing fevers have been reported, notably by Hammer.[29] The inexorable progressive course toward a fatal termination is

29. Hammer: Primäre Sarcomatose Ostitis mit chronischem Ruckfallsfieber, Virchows Arch. f. path. Anat. **137**:280, 1894.

the only factor in which it is at variance with an infectious disease, and harmonizes with malignant tumors. There is no disease caused by any known bacterium which is so invariably fatal; especially is this true of chronic diseases. In this respect it is somewhat comparable to rabies, caused by an as yet unknown virus, and practically invariably fatal unless previously protected by inoculation.

In 1898 Sternberg [28] promulgated a theory as to the tuberculous nature of the disease. He still holds to that, perhaps more tenaciously than ever. In his first series of fifteen cases, ten showed associated tuberculosis. In his latest article,[16] in 1925, he quotes considerable experimental work from the literature which tends to show the rela-

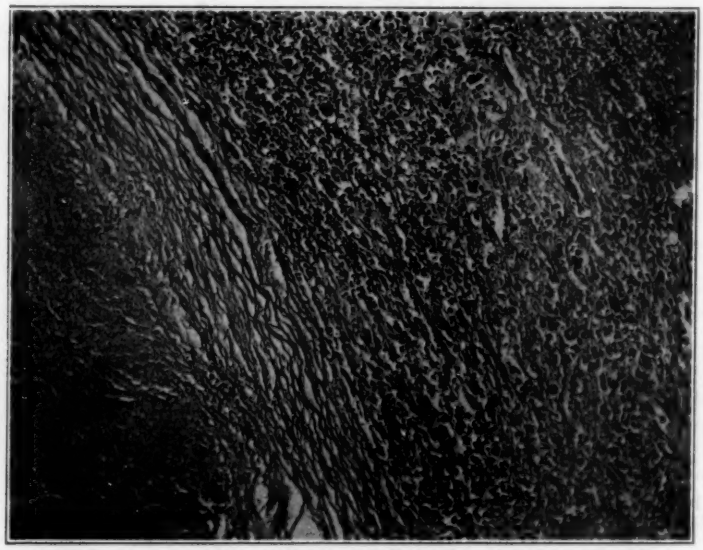

Fig. 10 (case 1).—Section of lymph node from prevertebral mass. A remnant of fairly normal lymphoid tissue is seen in one corner, then a zone of typical Hodgkin's disease, followed by a narrow zone of hyalinized connective tissue which immediately surrounds a large area of caseation necrosis.

tionship of tuberculosis to this disease. Sticker and Lowenstein [30] are cited by him as having injected Hodgkin's material into guinea-pigs and obtained characteristic lesions free from tuberculous lesions or tubercle bacilli, but from subsequent transplants into other guinea-pigs obtained typical tuberculosis histologically and culturally. Baumgarten [31] is shown to have obtained similar positive results. However, Sternberg

30. Sticker and Lowenstein: Ueber Lymphogranulomatose, Lymphomatose und Tuberkulose, Zentralbl. f. Bakteriol., Parasitenk. u. Infektionsk. Orig. **55**:267, 1910.

31. Baumgarten, P.: Ueber das Verhaltnis der Lymphogranulomatose zur Tuberkulose, Munchen. med. Wchnschr. **61**:1545, 1914.

also quotes Ceeler and Rabinowitsch,[32] Kraus [33] and Lubarsch [34] as not convinced as to the tuberculous etiology, and in fact more or less opposed to it.

I am not in accord with Sternberg in his tuberculous theory. Too many excellent workers have been unable to substantiate his observations. In my necropsy series, as in the experience of most of the observers, the great majority of cases are entirely unassociated with tuberculosis. When they have been so associated, the tuberculous involvement is generally more recent and is of the miliary type, suggesting a secondary invasion spread from some previous focus, and superimposed on the Hodgkin's disease. The tissues of Hodgkin's disease show no tuberculous lesions nor can the bacillus be demonstrated histologically. Most experimenters have been unable to infect animals either with tuberculosis or with Hodgkin's disease by inoculating them with Hodgkin's

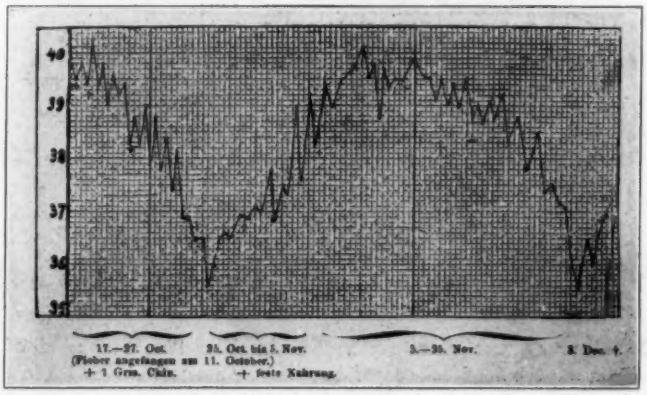

Fig. 11.—Temperature chart from case 3 reported by Pel in 1887.

tissues from excised glands that were free from a complicating tuberculosis. Cunningham and McAlpin [35] were unable to transmit Hodgkin's disease experimentally to anthropoid apes and other monkeys. Such negative results are certainly at variance with those obtained by inoculating with true tuberculous tissues. The few positive results reported can easily be explained by a coexistence of the two diseases.

It is also possible that glandular tuberculosis is more common in the locality from which Sternberg draws his experience. He tries to explain

32. Ceeler, N. W., and Rabinowitsch, L.: Ueber Lymphogranulomatose und ihre Beziehung zur Tuberkulose, Ztschr. f. Tuberk. **27**:175, 1917.

33. Kraus, F.: Lymphogranulomatose, Berl. klin. Wchnschr. **55**:705, 1918.

34. Lubarsch, O.: Ueber Lymphogranulomatose, Berl. klin Wchnschr. **55**:708, 1918.

35. Cunningham and McAlpin: Experiments with Hodgkin's Disease, Arch. Int. Med. **32**:351, 1923.

the difference in the clinical and pathologic course of Hodgkin's disease from that of tuberculosis by two factors; a greater resistance in the host, or a lesser toxicity of the bacillus, will result in Hodgkin's disease. To try to harmonize such a concept with the course of Hodgkin's disease seems to be contrary to ordinary logic and reason. Why should a host with an increased resistance or a bacillus that is attenuated always and invariably result in death, while a lowered resistance of the host or a more virulent type of the infecting bacillus will so frequently result in a complete cure? About 90 per cent of those with tuberculous infection of the "more virulent type" recover, while not one affected with the "more attenuated type" has been known to get well.

Another organism, a pseudodiphtheria or diphtheroid bacillus, frequently has been associated with the etiology of Hodgkin's to such an extent that it has been given the name of *Bacterium hodgkini*. This is a pleomorphic, non-acid-fast, but antiformin-fast, organism, first described by Fraenkel and Much.[36] It received the support of Sternberg, since it

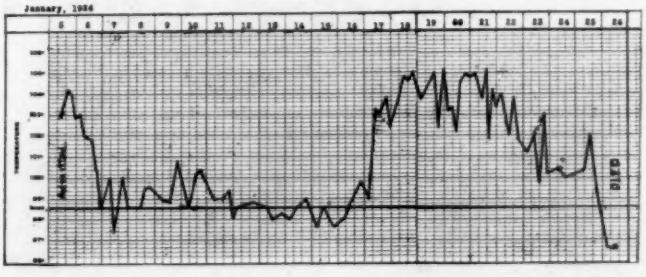

Fig. 12.—Temperature chart from case 1. The twelfth period of apyrexia extended over a period of ten days, but complete apyrexia was present during only four days. Death occurred on the tenth day of the thirteenth attack of fever. (Cf. fig. 11.)

was interpreted to be an anomalous type of tubercle bacillus. Bunting and Yeates,[37] de Negri and Mieremet,[38] and others, especially the first, strongly emphasized the specific relation of this organism to Hodgkin's disease. However, it has been convincingly shown by Bloomfield,[39] Favere and Colrat,[40] and others, that there is no special relation between

36. Fraenkel and Much: Bemerkungen zur Aetiologie der hodgkinsche Krankheit und der Leukemia lymphatica, München. med. Wchnschr. 1910, no. 13, p. 685.

37. Bunting and Yeates: Cultural Results in Hodgkin's Disease, Arch. Int. Med. **12**:236, 1913.

38. de Negri and Mieremet: Zur Aetiologie der malignen Granuloms, Zentralbl. f. Bakteriol., Parasitenk. u. Infektionsk., Orig. **68**:292, 1913.

39. Bloomfield: The Bacterial Flora of the Lymphatic Glands, Arch. Int. Med. **16**:197, 1915.

40. Favere, M., and Colrat, A.: Pathogenesis of Lymphogranulomatosis, Paris méd. **55**:177, 1925.

this organism and Hodgkin's disease, and that identical organisms have been found in lymph nodes from a great variety of sources both normal and pathologic. Lukes and Jelinek [41] found Much's granules in three of six cases of Hodgkin's disease, but they also found them in three of eleven controls in which neither tuberculosis nor Hodgkin's disease was present.

More recently, Kuczynski and Hauck,[42] in 1923, found inclusion bodies within the so-called Dorothy Reed cells, or, as they designate them, the SRZ (Sternberg's Riesenzellen), which are the characteristic cells of Hodgkin's disease. These characteristic cells they claim are not found anywhere in the normal body. They consider them as the "Virus-zellen" of this disease, as the carriers of the infection. They show numerous figures of the cells containing inclusion bodies which they

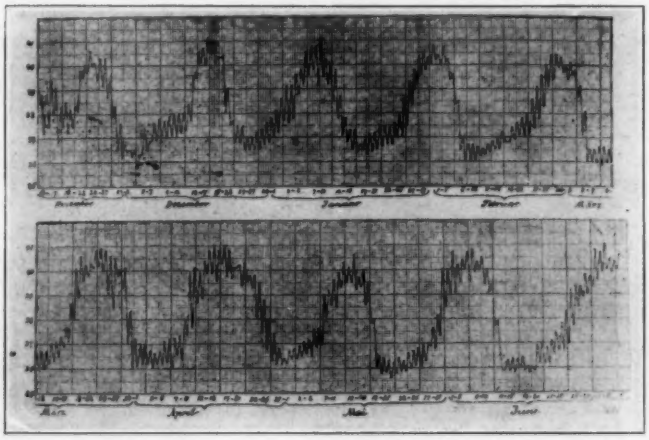

Fig. 13.—Temperature curve from case reported by Ebstein in 1887.

interpret as the parasites in different stages of growth and degeneration. They believe that the virus is a type of "Pilzinfektion," one of the higher bacteria intermediate between tuberculosis and actinomycosis. They hold that the morphology of this organism fits in and helps explain many of the forms of organisms previously described. This work, however, interesting and pregnant with possibilities, needs further confirmation.

Many of the conclusions reached by Kuczynski and Hauck coincide with my own views on the etiology of Hodgkin's disease. I agree with them that Hodgkin's disease is definitely an infectious granuloma in no way related to the etiologic agent of tuberculosis and that its exciting

41. Lukes and Jelinek: Etiology of Lymphogranulomatosis, Čas. lék. česk. **64**:728, 1925; abstr. J. A. M. A. **85**:236 (July 18) 1925.

42. Kuczynski, M. H., and Hauck, G.: Zur Pathogenese des Lymphogranuloms, Ztschr. f. klin. Med. **99**:102, 1923.

cause differs from any organism hitherto described. However, there are certain features in some cases of Hodgkin's disease that are not satisfactorily explained by the causative agent as advanced by them, namely, the peculiar type of relapsing fever and the marked eosinophilia. This fact, together with the nontransmissibility of the disease to other animals, militates against the theory that the causative agent is a vegetable parasite. Practically all known chronic relapsing types of fever are caused by animal parasites, as, for instance, malaria, trypanosomiasis, relapsing fever, kala azar, etc. The same holds true in regard to the eosinophilia which is also found associated with animal parasitic infections and infestations, as for example, trichiniasis, filariasis, trypanosomiasis and helminthiasis. Tuberculosis and other known bacterial

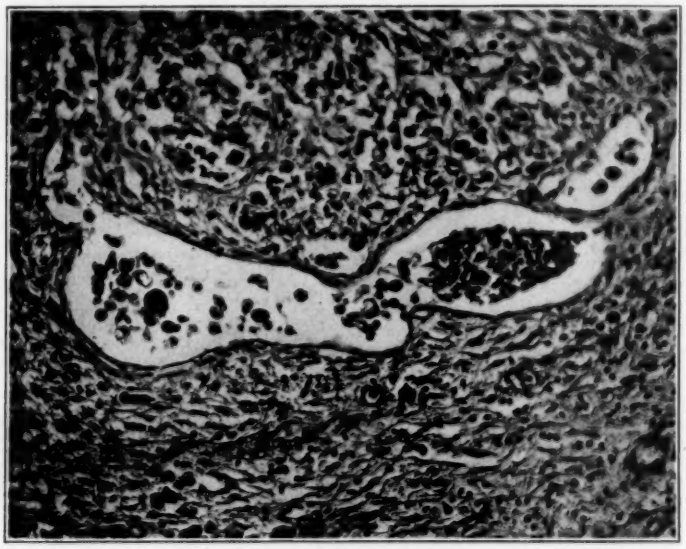

Fig. 14.—Section from lymph node showing reticulo-endothelial hyperplasia and the accumulation of masses of characteristic lymphogranulomatous cells within lymph spaces. Some of the sections showed this in great abundance.

infections never produce any definite eosinophilias unless it be through an allergic reaction as in bronchial asthma. Another objection to their plant parasitic theory is derived from their description and drawings of the causative agent. The indefinite pleomorphic cellular inclusions which they describe correspond much more closely to animal parasites or the cellular reactions to animal parasites. Moreover, a further objection to their Pilzinfektion is to be found in their own admission, on page 125: "There is only one difficulty, namely, the impossibility to demonstrate the micro-organisms in the cells, by Gram's stain—if our classification is correct, the micro-organisms should retain the anilin dye during

the process of decoloration." It is significant that they were unable to use the usual bacterial stain, the Gram stain, for demonstrating their organisms.

To sum up, I hold the theory advanced by Kuczynski and Hauck questionable, because the plant parasitic theory does not fulfil all the requirements of the etiologic agents of Hodgkin's disease; i. e., it does not fully explain the peculiar relapsing type of fever, the eosinophilia, the nontransmissibility to animals. The type of the inclusion bodies and the character of the staining reaction are also disturbing factors in their theory.

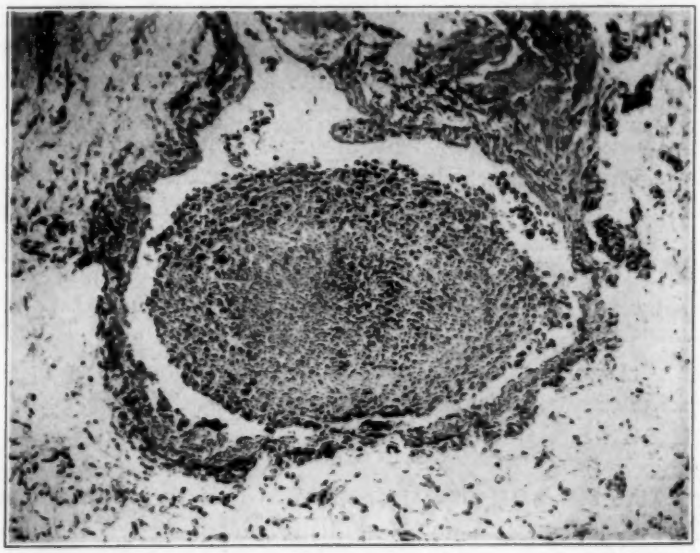

Fig. 15.—Section of lymph node showing rather large vein filled with a mass of lymphogranulomatous cells. Some of the giant cells are plainly visible. There is a beginning necrosis in the center of the mass. Invasion of the veins may explain the metastatic nodules in the lungs.

These objections hold equally true for all known bacterial etiologic agents of whatever type. If, however, I might interpret the cell inclusions described by Kuczynski and Hauck as being animal parasites or cellular reactions to them, I can conceive of these animal parasites as fulfilling all the requirements mentioned above for a causative agent of Hodgkin's disease.

SUMMARY

Hodgkin's disease is twice as common among males as among females. Fifty per cent of the cases occur during the second and third decades of life, although cases can occur in practically all ages. The average duration of this disease is under two years.

An associated infection with tuberculosis is not infrequent. The retroperitoneal and prevertebral lymph nodes are frequently involved, in our series exceeding that of the cervical nodes. The involvement of the spleen is a characteristic feature of this disease, and, contrary to the general opinion, this enlargement may at times be enormous. Involvement of the vertebrae may lead to a diagnosis of Pott's disease. No tissue or organ of the body is exempt from involvement.

The characteristic histologic picture is identical for every organ and tissue of the body. The Dorothy Reed cells or Sternberg's giant cells are characteristic of the disease.

The blood picture is not characteristic. However, some cases present marked eosinophilic leukocytoses, and this when associated with an enlarged spleen or enlarged lymph nodes is helpful in suggesting a correct diagnosis. A severe anemia of the secondary type is present in practically all cases in the terminal stages of the disease.

Some cases of Hodgkin's disease present characteristic types of chronic relapsing fever which probably constitute an integral part of the syndrome and are not due to secondary infections. A case of Hodgkin's disease with Pel-Ebstein type of fever is here reported which is unique in the regularity of the recurrences of the febrile attacks.

Pruritus is a common cutaneous manifestation in Hodgkin's disease, occurring in from 10 to 20 per cent of the cases. It may appear early, at times as an initial symptom, and may precede by months or even years the appearance of any visible skin lesions, when such lesions occur.

CONCLUSIONS

Hodgkin's disease (lymphogranulomatosis) is an entity anatomically as well as clinically. It is an infectious granuloma caused by an organism not yet identified.

Reasons are here presented to suggest that the etiologic agent is probably an animal parasite.

Neither tuberculosis nor the tubercle bacillus bears any etiologic relationship to this disease.

Caseation necrosis may be extensive in the lymph nodes of Hodgkin's disease and may thus resemble the necrosis of tuberculosis and lead to a mistaken diagnosis.

The pseudodiphtheria bacillus—*B. hodgkini*—has no causal relationship to this disease.

The prognosis of this disease is always hopeless. No chronic infectious disease caused by any known bacterium is so invariably fatal.

Roentgen-ray therapy may cause temporary symptomatic relief, but apparently has no effect on the progress of the disease.

An incontrovertible diagnosis can be established only through a biopsy.

DISCUSSION

DR. T. HOMER COFFEN, Portland, Ore.: Dr. Barron's paper centers around three points, first the condition as an entity, both clinically and pathologically; second, the etiology, and third, the prognosis. Nothing has been added to the pathology of the disease since the time of Sternberg in 1898 and Reed in 1902. Confusion as to the diagnosis and recognition of the disease has resulted from varying terminology which has been used in describing conditions involving chronic enlargement of the lymph glands. That the recurrent and relapsing type of fever should be considered a part of the disease and not due to secondary infection was brought out by Pal and Ebstein and is emphasized in the remarkable case presented by Dr. Barron. The fact that in the acute stages of the disease with the rise of fever there is a marked rise in temperature over the enlarged glands is further evidence in favor of the inflammatory nature of the disease. The caseation necrosis, a confusing factor, has been shown to be due to conditions other than tuberculosis, although Sternberg in a publication in 1925 still favors the tuberculous nature of the condition. The neoplastic theory of the disease seems sufficiently refuted to require no comment. While animal parasites as etiologic factors are theoretical, the postulates which rather favor this view are: first, the periodicity of the relapsing type of fever; second, the absence of proof of bacterial infection or neoplastic nature of the disease; third, the presence of eosinophils as a very frequent accompaniment; fourth, recent observations of amebas by Koefoed.

DR. EUGENE S. KILGORE, San Francisco: My experience with the radiation treatment of Hodgkin's disease coincides with that reported by Minot and others, namely, that the roentgen ray does not usually prolong life, except at times, in the emergency relief of pressure on the trachea, etc., but it does, as a rule, not only relieve distress but also materially prolongs the period of economic usefulness.

DR. MOSES BARRON, Minneapolis: There are many points of interest that I could not give you on account of lack of time. Dr. Minot came to the same conclusions in regard to leukemia as I have in regard to Hodgkin's disease, that is, that the patients are made more comfortable through roentgenotherapy, but life is probably not prolonged. The etiology of Hodgkin's disease has not been established, though a great deal of work has been done since Carl Sternberg, in 1898, tried to show the relationship of this disease to tuberculosis. A little later he himself felt that he had stated the relationship a little too strongly, but in his most recent publications he seems, again, to be enthusiastic in regard to his theory that Hodgkin's disease is due to some form of tubercle bacillus. I cannot quite see his method of reasoning. In order to explain the development of Hodgkin's disease from tubercle bacilli, he assumes that the organism is of the attenuated type or that the host has an increased resistance. It is difficult to understand how an attentuated type of organism or an increased resistance in the host will invariably prove fatal within a few years, while an infection with a more virulent type of organism or a lower resistance in the host will go on to recovery in about 90 per cent of the cases. Other etiologic agents have been described by Fraenkel and Much, deNegri and Mieremet, Bunting and Yeates and Kuczynski and Hauck. The organisms described by the first three are the diphtheroid bacilli which have been conclusively eliminated as etiologic agents by Bloomfield and others. The organism of Kuczinski and Hauck deserves a little more consideration. They find that intracellular bodies in the so-called Riezencellen of Sternberg are the so-called

Dorothy Reed cells. They show excellent pictures of these organisms. They feel that this is the true virus of Hodgkin's disease. As Dr. Coffen pointed out, there are certain reasons why bacteria even of the higher forms do not fulfil the requirements of the etiologic agents of Hodgkin's disease. However, if one should use the pictures of Kuczynski and Hauck and assume that the organism which they describe is either an animal parasite or the cellular reaction to an animal parasite, these would then fulfil all the requirements of a true causative agent. There is reason to believe that an unknown animal parasite is probably the cause of Hodgkin's disease.

ADENOMA OF THE SUPRARENAL*

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BALTIMORE

In the course of routine examination of the viscera at necropsy, solitary, more or less circumscribed, soft yellowish or reddish tumor masses are occasionally found in or arising from the cortex of the suprarenal.

The circumscription of these masses, together with their atypical and adenomatous structure, serves to indicate their neoplastic character and to place them in the group of benign glandular tumors or adenomas. Concerning the latter point and with reference to the terminology of tumors of the suprarenal cortex in general, there has been considerable controversy, for embryologically the cortex of the gland is mesodermal in origin, arising as a series of buds from the celomic epithelium covering the medial upper surface of the cephalic third of the wolffian body. Adami consequently has employed the term mesothelioma for tumors of the suprarenal cortex, recognizing that tumors of adenomatous, carcinomatous or sarcomatous nature may arise from these cells. Woolley,[1] Meakins,[2] and Jores[3] have observed sarcomatous metastases from adenomatous tumors of the suprarenal cortex. Yet, as Ewing[4] points out, the acquired epithelial characteristics of the cells in the type of growth under discussion so predominate that the term adenoma seems permissible.

Suprarenal adenomas are unquestionably rare. Kelynack,[5] in a series of 1,500 necropsies, observed but three cases. The tumors are usually unilateral and solitary, though occasionally bilateral and multiple growths are observed. They arise in the cortex of the gland, often apparently from the zona fasciculata, and are usually well circumscribed, although not commonly encapsulated. These tumors are soft, yellowish or reddish, and vary in size from a few millimeters up to, in exceptional cases, quite large masses which destroy the gland.

The histology varies from an almost exact reproduction of cortical tissue to glandlike spaces or alveoli, lined by cylindric or cuboidal cells

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* From the Department of Pathology, University of Maryland School of Medicine.

1. Woolley: Tr. A. Am. Phys. **17**:627, 1902.

2. Meakins: Proc. New York Path. Soc. **9**:19, 1909.

3. Jores: Deutsche med. Wchnschr. no. 9, 1894, p. 208.

4. Ewing: Neoplastic Diseases, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 768.

5. Kelynack: Edinburgh. M. J. **2**:263, 1897.

and possessed of a lumen. The fibrous stroma may be abundant or sparse, consisting merely of thin-walled capillaries. As adenomas, they do not commonly give metastases, but malignant transformation is probably of frequent occurrence.

In a number of cases of cortical suprarenal tumors, precocity in sexual development or the acquisition of opposite secondary sex characteristics have been reported. Auvray and Pfeffel [6] described a large cortical growth which they called an adeno-angiolipoma in a case of pseudohermaphroditism, while Tuffier [7] observed masculine characteristics in a woman 62 years of age, in whom large bilateral tumors derived from the suprarenal cortex were found. Jump, Beates and Babcock,[8] Baldwin,[9] Gregory,[10] and others report cases of sexual precocity in children with malignant cortical suprarenal tumors.

In a study of the results of the 1,190 necropsies performed at the University Hospital, three cases of adenoma of the suprarenal have been observed.

REPORT OF CASES

CASE 1.—A white woman, aged 44, admitted to the hospital in diabetic coma, died as a result of a complicating infection.

Left Suprarenal: The gland was enlarged, measuring 6 by 5 cm., with an average thickness, not including the tumor, of 0.5 cm. On the anterior surface, just above the hilum, a rounded, projecting tumor mass was seen. This tumor measured 3.2 by 2.5 by 2 cm. It was well circumscribed and could be partially lifted from the surface of the suprarenal, from which it was in part separated by a glistening filmlike membrane. The outer free surface of the growth was rounded and somewhat nodular. On section, it was seen to be yellowish mottled by tiny dark red areas of hemorrhage. The tumor was intimately connected with the suprarenal cortex by a thin stalk of tissue similar in appearance to that of the growth. That portion of the suprarenal immediately beneath the tumor was thinned out to approximately 0.2 cm. The architecture of the suprarenal elsewhere appeared normal.

Microscopic Examination: The tumor presented no capsule except along its outer border, where a few strands of fibrous connective tissue lay against the tumor cells. At the area of its attachment to the suprarenal, the growth was contiguous with spheroidal groups and anastomosing columns of columnar cells, having the arrangement and morphology of the normal cortex. Between the normal and the tumor tissue, there was a sharp transition, for in the tumor an abundant, more or less hyaline appearing, stroma divided the tissue into irregular alveoli. In areas the stroma was less abundant and quite delicate, and consisted for the most part of thin walled, blood filled capillaries. The alveoli varied considerably in size; they were completely filled with large, pale, cuboidal or rounded

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6. Auvray and Pfeffel: Bull. et mém. Soc. anat. de Paris **86**:305, 1911.
7. Tuffier: Bull. Acad. de méd. Paris **78,** 1914.
8. Jump, Beates and Babcock: Am. J. M. Sc. **147**:568, 1914.
9. Baldwin, J. F.: Adrenal Precocity, J. A. M. A. **63**:2286 (Dec. 26) 1914.
10. Gregory: Proc. Royal Soc. Med. **75**:50, 1921.

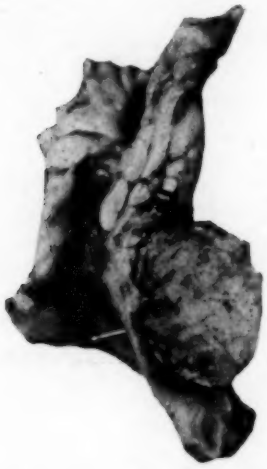

Fig. 1.—Suprarenal tumor in case 1.

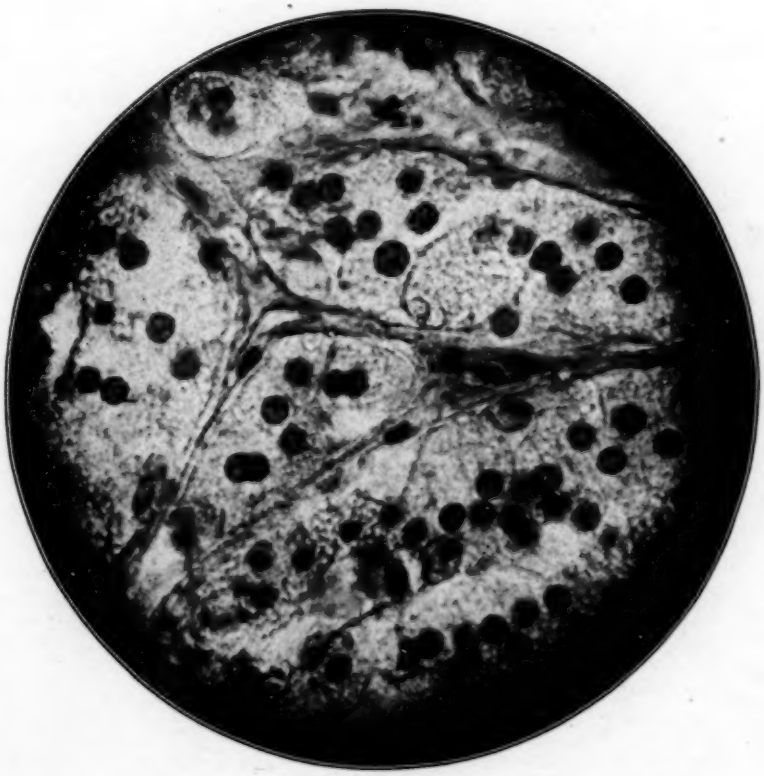

Fig. 2.—High power magnification of tumor in case 1.

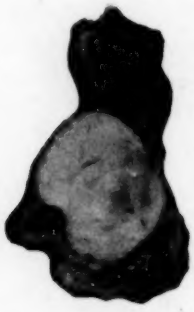

Fig. 3.—Suprarenal tumor in case 2.

Fig. 4.—Photomicrograph of tumor in case 2.

cells, whose protoplasm was finely reticulated and moderately fatty. The cell nuclei were spheroidal and rich in chromatin; mitotic figures were not observed.

The right suprarenal was normal.

CASE 2.—A colored woman, aged 42, admitted to the hospital because of fever, weakness and pain in the left leg, apparently died of sepsis.

The left suprarenal measured 4 by 2.5 cm., with an average thickness, not including the tumor, of 0.5 cm. A soft, rounded tumor mass measuring 2 by 1.5 by 1.3 cm. lay in a hollow curve of the distorted gland. The tumor was well circumscribed; about one-fourth of its surface was exposed. It was continuous with the cortex of the suprarenal through a small stalk. The gland immediately beneath the tumor was reduced to a width of 0.1 cm. On section the tumor was soft, yellowish and homogenous, and except at the site of origin of the tumor, the architecture of the gland appeared normal.

Microscopic Examination: Sections of the tumor and attached suprarenal tissue showed normal structures on either side of the tumor attachment. Beneath the point of attachment the cortical and medullary tissue was atrophied. From the inner side of the gland and apparently arising from the zona fasciculata, was a mass that on its inner and lateral borders lay in close approximation to the suprarenal, although sharply defined from it. The outer exposed surface of the tumor was covered by several layers of fibrous connective tissue; otherwise there was no definite capsule. The tumor was composed of irregularly arranged anastomosing columns of polyhedral cells, held by a delicate vascular connective tissue stroma. The cells were pale and finely granular, and contained fat droplets. The cell outlines were rather indistinct. The nuclei were spheroidal; some were hyperchromatic, others were vesicular.

The right suprarenal was normal.

CASE 3.—A colored man, aged 55, admitted to the hospital because of inability to void urine, died of an ascending urinary tract infection.

The right suprarenal measured 5 by 2.3 by 0.4 cm. A soft, circumscribed tumor mass, which measured 2.6 by 2.2 by 2 cm., arose by an attachment from its upper surface. The suprarenal beneath the tumor was thinned out. On section the tumor was yellowish, and its center was soft.

Microscopic Examination: Sections showed a sharp transition from the normal cortical tissue at the site of the tumor attachment and the tumor tissue. The tumor was composed of irregular alveoli containing pale, finely granular, polyhedral cells. Fine droplets of fat were seen in the protoplasm. The nuclei were spheroidal and many of them were hyperchromatic. The fibrous stroma was for the most part delicate and carried thin walled blood vessels.

The left suprarenal was normal.

COMMENT

In the three cases here reported, benign glandular tumors of the suprarenal cortex have been observed. The type of cell and cell arrangement are more or less similar to those of the suprarenal cortex.

The histology of the tumors in cases 1 and 3 is similar, and the cell arrangement is like that of the zona glomerulosa, while in case 2 the arrangement of the cells suggests the zona fasciculata as the point of origin of the tumor. The patients were all over 40 years of age. There

Fig. 5.—Suprarenal tumor in case 3.

Fig. 6.—Photomicrograph in case 3.

were two women and one man. The histories disclosed no evidence of cortical hyperactivity, such as has been reported in cases with larger and more actively growing tumors. Marked hyperactivity was unlikely because of the small sizes and slow growth of the tumors observed. Probably this particular type of neoplasm will continue to be recognized only at necropsy.

HEMOPOIETIC EFFECT IN RABBITS OF INTRAVENOUS INJECTION OF CELLS, NUCLEI AND NUCLEIC ACIDS FROM BLOOD OF FOWLS*

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The present study was begun as an attempt to follow in detail on normal and splenectomized rabbits, by histologic methods, the fate of nucleated red blood cells introduced into the blood stream, with especial reference to the rôle in their destruction, of certain cells of the spleen, liver and other organs. It soon became apparent that profound changes were produced in the blood picture by this treatment in the number of both erythrocytes and leukocytes, and also in the proportions of certain types of the latter. Attention was therefore directed, as part of the main problem, toward an effort to analyze the cause of these variations. The results of this part of the study are here presented. They are based on experiments with thirty-three rabbits.

The cells to be injected were prepared by drawing blood from adult fowls into sodium oxalate and centrifugalizing to separate the plasma. They were then washed four times with saline solution, and 8 cc. of the washed and centrifugalized cells were diluted with sodium chloride of proper strength to produce from 12 to 15 cc. total volume of cells suspended in a 0.9 per cent solution of sodium chloride. Rabbits of 5 to 5½ pounds (2.3 to 2.5 Kg.) in weight were used, and injections with the suspension were made through the lateral ear vein.

The rabbits soon showed the effects of profound shock. Within fifteen minutes after injection the respiration became very rapid, the heart rate increased, and the animal became lethargic. Blood counts indicated a sharp drop in the erythrocyte count, so that most of the animals showed a drop from 6,200,000, which was the average, to as low as 3,500,000, within from three to five hours after the fowl blood cells were administered. The blood counts were made at intervals of from thirty minutes to one hour during the first day, and then at twenty-four hour intervals for one week or more. Following this, counts were taken at intervals of from three days to one week as long as the animals were kept under observation, ranging from four weeks to three months, and in one case, more than a year. There was considerable variation both in

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the normal count and in the level to which the cell number dropped, but in all cases there was a loss varying between 22.7 and 43.5 per cent below normal (table 1). This decrease in the number of cells was accompanied by severe hemoglobinuria, which usually appeared within thirty minutes after injection and continued for from twelve to sixteen hours. The hemoglobinuria was evidently associated with the destruction of the injected cells. These cells disappeared from the circulation in from one to four hours after injection, but could be recognized in the spleen, bone-marrow and liver up to from twelve to sixteen hours after they were introduced. These observations on the hemoglobinuria and the duration of the injected cells in the spleen are in agreement with the results obtained by Addison,[1] who, however, did not record any data for the other organs in this particular.

TABLE 1.—*Effect of Injecting Whole Washed Chicken Blood Cells Into the Blood Stream of Rabbits* *

These tables are illustrative only, representing a typical instance from a series of nine rabbits, in the case of table 1, and of three rabbits in table 2.

Rabbit	Erythrocytes	Leukocytes	Time of Count After Injection	Immediate Effect of Dose
II-5 *	6,200,000	7,000		
	5,600,000	8,000	30 minutes	Initial depression, hemoglobinuria and rapid respiration
	5,000,000	9,000	2 hours	
	3,500,000	20,000	3 hours	
	7,200,000	22,000	30 hours	
	8,500,000	27,000	40 hours	
	7,800,000	15,000	5 days	
	7,750,000	14,500	10 days	
	8,400,000	13,000	14 days	
	8,000,000	13,500	35 days	
	7,600,000	15,000	65 days	
	7,400,000	22,000	90 days	

* The count before injection.

The low point in the red cell count was reached from three to five hours after injection in all normal rabbits. Then began a more or less rapid increase in the number of cells, so that within from twenty-four to forty-eight hours the count had reached normal and in some cases had passed beyond this point. After the first period of from twenty-four to forty-eight hours, the curve of increase was less pronounced, although it continued until the maximum count was reached in from forty to seventy-two hours. With slight variations, it continued above normal as long as the animals were kept under observation—in one case for more than one year. This result is in contrast with that obtained by Leake and Leake,[2] in whose animals the cell count returned to normal within a few days after administration of saline extracts of spleen and of red bone marrow was discontinued.

1. Addison, W. H. F.: Am. J. Anat. **26**:437, 1920.

2. Leake, C. D., and Leake, Elizabeth W.: J. Pharmacol. & Exper. Therap. **22**:75, 1923.

The principal factor responsible for this decrease in cell count appears to have been the mechanical blocking of the capillaries by the injected chicken cells. These have an average size of 12.1 microns by 7.2 microns,[3] as against the average diameter of 7.16 microns of the rabbit erythrocytes. As a test of this interpretation, we injected duck blood cells, which have an average size of 12.9 microns by 8 microns, or 6.6 per cent greater length and 11 per cent greater breadth than the chicken cells. Injection of duck cells produced even more marked symptoms and rapid fall of blood count than did the chicken blood cells. One of the rabbits receiving these injections died after ninety minutes of marked depression and progressive dyspnea. A second showed a drop in cell count from 6,027,000 to 3,756,000 in five hours. A third rabbit whose symptoms were similar to the preceding was killed two hours after injection with the duck cells. The lungs were fixed in situ, and were subsequently embedded in celloidin. Sections stained with hematoxylin and eosin showed a congestion of duck cells on the arterial side of the capillaries, but very few on the venous side. The initial peripheral anemia and other symptoms such as increased heart rate and dyspnea, all of which were present in greater degree in the rabbits receiving the duck cells, were evidently due to the mechanical blocking of the capillaries.

In splenectomized rabbits the same general phenomena were noted, but the initial drop was not so pronounced and also it did not reach its minimum until from four to six hours after injection, instead of from three to five hours in the normal animal. The return to and beyond normal was also delayed. As in normal rabbits, the count did not remain at the preinjection normal, but continued to climb rapidly at first, and then more slowly until a point 24 to 55 per cent above the normal was reached and maintained as long as the animals were kept under observation, i. e., from a few days to ten weeks.

Determination of the factor responsible for the increased count in red cells was attempted by injecting separately the several constituents of the fowl cells. Hemoglobin from an amount of chicken blood corresponding to that used in the whole blood cell injections, namely 8 cc., was diluted to 15 cc. with a 0.9 per cent solution of sodium chloride and administered as before. As a check, hemoglobin from horse blood obtained in a similar manner was also injected. The rabbits given chicken hemoglobin showed marked depression in from fifteen to twenty minutes. There was pronounced dyspnea and rapid heart, but only a slight drop in blood count. This was followed by return to normal blood count in from twenty-four to forty-eight hours, but no increase beyond this point occurred, as with the rabbits treated with whole blood cells. Hemo-

3. Bohm, Davidoff and Huber: Textbook of Histology, 1919.

globinuria was marked in all, but appeared more pronounced in the animals receiving injections with chicken hemoglobin. In other respects the horse hemoglobin produced more marked symptoms.

To determine the effect of the stroma substance, one series of rabbits was given a dose of 8 cc. of centrifugalized and washed horse blood cells, diluted to 15 cc. and made isotonic with a solution of sodium chloride. These animals showed an initial hyperexcitability immediately after the injection, but in from one to one and one-half hours depression came on. After twenty-four hours, there was an increase in leukocyte count, which persisted in an acute stage for about twenty-four hours longer. It returned to normal within a few days. All of these rabbits showed a slight increase in the number of erythrocytes for a few days, but not enough to appear significant. The conclusion seems warranted that the stroma and hemoglobin do not have any hemopoietic effect in our animals. This is in agreement with the results obtained by Robertson,[4] who introduced laked blood cells into the circulation of rabbits, without evidence of increased activity of the bone marrow. It also agrees with the experience of various workers with reference to hemoglobin.

The net results of the experimental procedure so far described indicate that the hemopoietic agent is resident in the nuclei of the cells, rather than in the stroma or hemoglobin. A preliminary injection of 1.5 per cent solution in 0.9 per cent sodium chloride of nucleic acids from yeast (Pfanstiehl) was accordingly made into four rabbits. Two of these animals received 15 cc. each, and two others 12 cc. and 8 cc., respectively, intravenously. One died almost immediately, apparently from embolism. The others showed a drop in red cell count, which in one rabbit reached 17 per cent below normal within twenty-four hours. In all, this was followed by an increased count from an average of 5,597,000 to an average for the three animals of 6,365,000 in three to four days, an increase of 6 per cent. The leukocytes also increased to a high point of 23,000, 15,200 and 25,000, respectively. A gradual return of both red and white cells to normal limits ensued, and the count became stabilized to about the preinjection normal in from eight to fifteen days. These results compare with those obtained by Leake [5] and his co-workers from introducing saline extracts of spleen and red bone marrow, both by mouth and intravenously.

The next step in our investigation appeared logically to be to obtain nucleic acids from the fowl blood cells themselves, and to administer these into a series of rabbits. This was done by extracting the nucleic acids from chicken blood cells by the method of Neumann.[6] The

4. Robertson, O. H.: J. Exper. Med. **26**:221, 1917.

5. Leake, C. D.: J. Pharmacol. & Exper. Therap. **22**:401, 1923. Leake, C. D., and Bacon, F. J.: Ibid. **23**:353, 1924. Also footnote 2.

6. Mathews, A. P.: Physiological Chemistry, ed. 4, 1925.

extracted and desiccated acids were then made up as a 2.57 per cent solution in a 0.9 per cent solution of sodium chloride, and 15 cc. of this solution was administered intravenously into each of three rabbits. Blood counts were made one, three and fourteen hours after the injection, and then at from twenty-four to seventy-two hour intervals for a period of from four to six weeks, as shown in table 2, which is typical.

There was no observable depression and no hemoglobinuria in these animals. They appeared as well and alert at all times after the administration of the nucleic acids as before. Rabbit number 3 of this series showed a slight drop in erythrocyte count after one hour, and this was further reduced after three and one half hours, but in all three animals

TABLE 2.—*Effect of Injecting Nucleic Acids from Chicken Blood Cells*

Rabbit	Erythrocytes	Leukocytes	Time of Count After Injection	Immediate Effect of Dose
VIII-1 *	5,840,000	8,000		
	5,884,000	8,000	1 hour	No depression or other signs of ill effect
	5,640,000	9,600	3 ½ hours	
	6,460,000	13,800	14 hours	
	6,526,000	14,266	48 hours	
	6,784,000	12,400	72 hours	
	6,920,000	14,200	4 days	
	6,768,000	14,400	5 days	
	7,304,000	13,200	7 days	
	7,680,000	13,200	10 days	
	7,544,000	14,354	13 days	
	7,396,000	10,420	18 days	
	7,864,000	8,000	25 days	

* The count before injection.

there was an increase in fourteen hours of from 550,000 to 620,000 in the number of erythrocytes, and of 5,000 to 8,200 in the number of leukocytes. Four days after the injection the number of red cells had increased from 18 to 26 per cent. Differential counts of the leukocytes indicated a large influx of myelocytes, so that this type of cell numbered from 26 to 32 per cent of the total leukocyte count. Both erythrocytes and leukocytes continued to increase for some time, as shown in the table, until the red cell count became more or less stabilized after about six days at a point from 25 to 32 per cent above the preinjection normal for the respective rabbits.

Leake and Bacon [5] conclude that spleen and bone marrow contain an erythropoietic agent. Many of the properties which they ascribe to this substance are also shared, apparently, by the nucleic acids administered by us, but with the exception that the hemopoietic agent used by Leake and his co-workers is inactivated by alcohol and ether. The nucleic acids from the fowl blood cells were obtained by the use of strong alcohol, according to the method of Neumann, as already indicated, so that presumably the lipins and lecithins at least were left in solution.

Moreover, Ackermann's [7] analysis of the nuclei of hen's blood shows 42.10 per cent of nucleic acids and 57.82 per cent histone. It appears improbable that any appreciable amount of lipins or lecithins could have been present in the material injected into our rabbits in the later experiments when we injected the nucleic acids, although when the whole bird cells were administered, in the earlier part of the work, these substances were present. It will also be recalled that the horse blood cells, which have the same general composition as fowl cells, less the nucleus, failed to produce hemopoiesis when administered, as did also the laked blood in Robertson's experiment, to which reference has been made. It therefore appears that the principal factor responsible for hemopoiesis in our animals is the nucleic acid which was administered. This serves in some manner to stimulate the hemopoietic centers, as shown by hyperplasia of the red bone marrow in all the animals thus treated which were subjected to necropsy. It is possible that there is also produced an increased resistance of the red corpuscles to the destructive agencies, so that the life of these cells is prolonged.

We have no suggestion, as yet, to offer in explanation of the relatively long duration of the high blood count in our rabbits after a single dose of nuclear material. Leake found only a temporary increase, with return to normal within a few days after administration of saline extracts of spleen and bone marrow was discontinued. Further work now in progress, it is hoped, will throw some light on this phase of the problem.

SUMMARY

The results of our experiments indicate that the initial marked drop in erythrocyte count which follows intravenous administration of whole fowl cells is due chiefly to the mechanical blocking of the capillary field by the injected cells, which are larger than the erythrocytes of the rabbit.

The early depression which occurs after the injection of the whole cells or of hemoglobin from corresponding amounts of blood, is due to the effect of the hemoglobin rather than to other constituents of the blood cells.

The agent which stimulates hemopoiesis appears to be the nucleic acids present in the nuclei of the bird cells rather than any constituent of the stroma or the hemoglobin.

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7. Ackermann, D., in Hoppe-Seyler's Ztschr. f. Physiol. Chem. **43**:299, 1904-1905.

Laboratory and Technical Notes

STUDIES ON A FLOCCULATION TEST FOR SYPHILIS

I. Comparative Results Obtained by Different Methods of Diluting Antigen *

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In a series of papers,[1] I have described a flocculation test for the serum diagnosis of syphilis and the results obtained in the examination of several thousand serums. This method, which was developed in the course of studies on the Meinicke reaction, differs from the latter test in certain essential features. These points of difference are concerned with the material used in the preparation of the alcoholic extract of heart muscle, and its standardization and dilution before adding to the serums to be tested.[2] An additional distinction from Meinicke's original method is the use of raw serum and the addition of glycerol to the diluted alcoholic extract.

Meinicke uses dried horse heart in the preparation of antigen, but equally good results are obtained with human or beef heart, as was shown by a comparative study of extracts prepared from these three tissues.[3] That the method of standardization proposed by Meinicke is unnecessary has been proved by testing many serums with antigens which showed a wide variation in the concentration of the alcohol soluble lipoids, without, however, obtaining a variation in results. Instead of adding one half volume of distilled water to the alcoholic extract and allowing this mixture to stand for one half hour before adding the required amount of 3 per cent sodium chloride solution, equally good results are obtained by adding the salt solution directly to the alcoholic extract. However, the manner in which the reagents are mixed influences the reaction in a marked degree, and it is this question which forms the subject of this paper.

The addition of glycerol in an amount which gives a 10 per cent solution of this reagent in the mixture of serum and antigen causes a more complete agglomeration of the colloids, and the floccules which are formed in positive reactions are increased in size and held in suspension in the liquid. The number of positive reactions is increased by using raw instead of inactivated serums without, however, the occurrence of false positives. The results of a detailed study of this question are comprised in a recent paper[3] and confirm observations previously made by Epstein and Paul.[4]

These various modifications have resulted in the development of a test which is much simpler than Meinicke's third modification, and which shows a stronger reaction due to the formation of larger floccules. Comparative studies of the Meinicke test and the flocculation test which I have proposed have shown close

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* From the Pathological Laboratory of Northwestern University, Chicago.

1. McGlumphy, C. B.: J. Lab. & Clin. Med. **9**:539 (May) 1924; J. Infect. Dis. **35**:540 (Dec.) 1924.

2. McGlumphy, C. B.: J. Infect. Dis. **35**:540 (Dec.) 1924.

3. McGlumphy, C. B., and Brandes, W. W.: J. Lab. & Clin. Med. **11**:459 (Feb.) 1926.

4. Epstein and Paul: Med. Klin. **17**:1118 (Sept.) 1921.

agreement with each other and also with the results of the Wassermann reaction. However, the results with the flocculation method have not been as specific as those obtained by the Wassermann test when both reactions were checked by the clinical diagnosis. Especially with the serums of patients treated for syphilis giving a ++ or +++ Wassermann reaction and in whom clinical evidences of syphilis have been present has the percentage of positive flocculation reactions been less than that obtained by the Wassermann test. Further studies have been made with the object of increasing, if possible, the percentage of agreement with the Wassermann test as well as a closer agreement with the clinical diagnosis.

Previous observation and experiments had demonstrated that a solution without opalescence was formed by adding an equal volume of glycerol to an alcoholic extract of heart muscle which had first been extracted with ether, mixing, then adding six parts of a 3 per cent solution of sodium chloride. Furthermore, careful observation showed that glycerol when added in this manner caused a delay in the appearance of floccules in positive serums. While the presence of glycerol delays the beginning of agglomeration of the colloids, yet after a period of from fifteen to eighteen hours the tubes containing positive serums show a stronger reaction than is obtained when glycerol is not present in the mixture. For this reason the presence of glycerol in an amount equal to 10 per cent of the total volume of antigen plus serum is desirable.

Recent experiments have demonstrated that the manner of diluting the alcoholic extract has a marked effect on the physical properties of the resulting mixture and also on the flocculating properties when added to syphilitic serum. It is a well recognized fact that the sensitiveness of the various antigens used in the Wassermann test is influenced by the manner of mixing the antigen and physiologic salt solution. This fact suggested that a similar principle might be involved in the flocculation reaction, and that a variation in the manner of diluting the alcoholic extract of heart muscle would also influence this reaction.

Some preliminary tests were made, and it was immediately recognized that a perfectly clear, a slightly opalescent or a markedly opalescent solution could be obtained by varying the method of mixing constant quantities of alcoholic extract, glycerol and 3 per cent sodium chloride solution. Further trial demonstrated that the percentage of positive and negative results varied according to the manner of preparing the dilutions. Following these observations a careful study was made of the results obtained by testing a number of syphilitic and nonsyphilitic serums with antigens prepared by diluting the alcoholic extract in different ways. The method of preparing the alcoholic extract and performing the flocculation test will be described.

PREPARATION OF ALCOHOLIC EXTRACT

Ten grams of heart muscle[5] which has been dried and pulverized are extracted three times with ether at room temperature. Approximately 90 cc. of ether should be used, and each period of extraction should continue for a period of from twelve to twenty-four hours, after which the ether is poured off and fresh ether added. The mixture should be shaken occasionally during the process of extraction. The third portion of ether having been decanted, the moist powder is allowed to dry at 37 C. until no odor of ether remains. Ninety cc. of 95 per cent alcohol is then added to the dry powder and the flask kept at 37 C. for from several days to one week. The solution of lipoids in alcohol occurs rapidly, and extracts produced by only twelve hours' extraction show a heavy lipoid content. The mixture is filtered and without standardization is ready for use. The ques-

5. A preparation of dried beef heart made by the Digestive Ferments Company, Detroit, Mich., was used.

tion of standardization has been studied by using an alcohol extract of heart muscle prepared as described but double this strength, and adding to serum antigen containing 0.05 cc., 0.1 cc. and 0.2 cc. of the alcoholic extract in each 0.8 cc. of the mixture of alcoholic extract, glycerol and 3 per cent sodium chloride solution. Tests made with these antigens containing different amounts of the alcoholic extract showed agreement in results as regards positive and negative reactions. Positive tubes containing the greatest concentration of the alcoholic extract showed the presence of more floccules and, therefore, the strongest reaction, since more lipoids are in solution and undergo flocculation.

DILUTION OF ALCOHOLIC EXTRACT

This procedure is of the greatest importance in the flocculation method, and the best results are obtained by adhering to a definite method to be described. The results obtained by other methods of dilution will also be tabulated. For each test, 0.1 cc. of the alcoholic extract, 0.1 cc. of glycerol and 0.6 cc. of 3 per cent sodium chloride solution are required. The amounts of the three ingredients for the required number of tests having been determined and mixed, 0.8 cc. of the mixture is added to from 0.2 to 0.3 cc. of serum. The antigen and serum are mixed well and the tubes kept at 37 C. Many serums which give a strong positive reaction will be recognized at the end of a few hours' incubation, especially with slight magnification, while the great majority of positive reactions are readily recognized with the naked eye after a period of from twelve to eighteen hours' incubation. This is only true of serums which have been mixed with an antigen diluted in a manner that yields the optimum results.

In these studies it has seemed advisable to designate the positive reactions as strong, plain and weak. A strong reaction shows the presence of large floccules while in a plain reaction the floccules are smaller, but are readily recognized without magnification. A weak reaction may be suspected without magnification and is readily recognized by the aid of a hand lens which should be used in routine examinations.

In these experiments five methods of diluting the alcoholic extract have been carried out, and a considerable number of serums giving a positive and others giving a negative Wassermann reaction have been tested simultaneously and under the same conditions. The antigens resulting from varying the manner of mixing the ingredients has been designated A, B, C, D and E. The manner of preparing these various antigens will be described, and the reactions obtained with a number of serums will be tabulated.

Antigen A: To the required amount of alcoholic extract 3 per cent sodium chloride solution is added drop by drop, shaking after each drop, until approximately one-half as much salt solution as alcoholic extract has been added. Then at once the remainder of the salt solution is added; after this has been shaken, glycerol is added and mixed well. This manner of mixing produces a solution of marked opalescence, but spontaneous flocculation does not occur even after a long period of standing. Careful observation and comparative tests have demonstrated that an antigen prepared in this manner yields the optimum results.

Antigen B: The alcoholic extract is placed in a container and the entire amount of the 3 per cent salt solution is added at once; the mixture is shaken, glycerol is added, and all the ingredients are well mixed. This mixture is somewhat opalescent.

Antigen C: To the alcoholic extract at once an equal volume of 3 per cent salt solution is added and shaken; the remainder of the sodium chloride solution is added and shaken, and then glycerol is added and mixed well. This mixture is less opalescent than antigen A, but more opalescent than antigen B.

Antigen D: To the required amount of sodium chloride solution the alcoholic extract is added drop by drop, shaking after each drop; glycerol is added and mixed well. This antigen is perfectly clear.

Antigen E: To the required amount of 3 per cent sodium chloride solution the alcoholic extract is added at once and mixed; glycerol is added and again mixed well. The resulting antigen is perfectly clear.

In the following tables are set forth the results obtained by testing a number of positive serums with antigens prepared as described. All of these serums gave a positive Wassermann reaction and a positive flocculation test with antigen A. The flocculation test was made before the serums were inactivated.

TABLE 1.—*Results of Testing Inactivated Serums with Various Antigens*

Inactivated Serums	Antigen A	Antigen B	Antigen C	Antigen D	Antigen E
1	Plain	—	—	—	—
2	Weak	—	—	—	—
3	Plain	Weak	—	Weak	Weak
4	—	—	—	—	—
5	Plain	Weak	—	—	—
6	—	—	—	—	—
7	—	—	—	—	—
8	Plain	—	—	—	—
9	Plain	Weak	Weak	Weak	Weak
10	Weak	—	—	—	—
11	Plain	—	—	—	—
12	Plain	Weak	Weak	Weak	Weak
13	Plain	—	—	—	—
14	Strong	Strong	Strong	Strong	Strong
15	Strong	Weak	—	—	—
16	Plain	—	—	—	—
17	Weak	—	—	—	—
18	Plain	—	—	—	—
19	—	—	—	—	—
20	Plain	—	—	—	—
21	Strong	—	—	—	—
22	Strong	Weak	—	—	—
23	Weak	—	—	—	—
24	Plain	Weak	Weak	Weak	Weak
25	Weak	—	—	—	—
26	Plain	—	—	—	—
27	Weak	—	—	—	—
28	—	—	—	—	—
29	—	—	—	—	—
30	Plain	—	—	—	—
31	Strong	Strong	Strong	Strong	Strong
32	Plain	Weak	Weak	Weak	Weak
33	Weak	—	—	—	—
34	Weak	—	—	—	—
35	Plain	—	—	—	—
36	Strong	Plain	Strong	Strong	Strong
37	Plain	—	—	—	—
38	Strong	Strong	Strong	Strong	Strong
39	Strong	Weak	Plain	Plain	Plain
40	Plain	Weak	—	—	—
41	Plain	Weak	—	—	—
42	Strong	Weak	—	Weak	Weak

After inactivation, the serums comprised in table 1 were then tested with antigens A, B, C, D and E. The marked superiority of antigen A is at once apparent when the table is studied. It will be noted that six serums in this table gave a negative flocculation test with antigen A after inactivation, but had given a positive reaction before inactivation. This is further confirmation of observations which I have previously published.

The serums comprised in table 2 were not inactivated, and while it is apparent that the best results were obtained with antigen A, the percentage of positive results with the other antigens is greater than was obtained by using inactivated serums. Serums giving a negative Wassermann and a negative flocculation reaction with antigen A were also negative with antigens B, C, D and E.

TABLE 2.—*Results of Testing Raw Serums with Antigens*

Raw Serums	Antigen A	Antigen B	Antigen C	Antigen D	Antigen E
1	Strong	Plain	Strong	Strong	Strong
2	Strong	Weak	Weak	Weak	Weak
3	Plain	—	—	—	—
4	Strong	Strong	Strong	Plain	Plain
5	Strong	Strong	Strong	Strong	Strong
6	Strong	Weak	Weak	Weak	Weak
7	Plain	—	—	—	—
8	Plain	—	—	—	—

COMMENT

The antigens resulting from these different methods of mixing the alcoholic extract, 3 per cent sodium chloride solution and glycerol, have been tested against a considerable number of syphilitic and nonsyphilitic serums, and the results have been compared with each other as well as with the results of the Wassermann test. While some positive serums gave an equally strong reaction with all the antigens studied, other positive serums, that is serums which gave a ++++ Wassermann reaction in addition to a strong positive flocculation reaction with antigen A, were generally weaker and in some cases frankly negative when tested with antigens B, C, D and E.

Reference to the tables shows that the best results were obtained with antigen A. Furthermore, this antigen shows the greatest degree of opalescence. It might be suggested that the greater the degree of opalescence, the more sensitive is the antigen. A study of the tables and reference to the appearance of the different antigens does not confirm this assumption. While antigens D and E, which are perfectly clear, show the same results, antigen C, which shows a degree of opalescence second to that of antigen A, gave a smaller percentage of positive results than was obtained by antigen B, although the latter is less opalescent than antigen C.

By diluting the alcoholic extract as in the preparation of antigen A, there is doubtless brought about a preliminary stage in the agglomeration of the colloids, and in this state the colloids are more rapidly and certainly brought to a stage of complete agglomeration, and appear as floccules in a clear or slightly opalescent menstruum according to the degree of the reaction. This final stage of agglomeration is brought about by the presence in syphilitic serum of some specific, but as yet undetermined, substance.

CONCLUSIONS

1. The percentage of positive and negative results with the flocculation test for syphilis is influenced by the manner in which the alcoholic extract of heart muscle is diluted with 3 per cent sodium chloride solution.

2. The optimum results are obtained by adding the salt solution to the alcoholic extract, drop by drop, and shaking after each drop, until an amount of the salt solution equal to approximately one half the volume of the extract has been added. The remainder of the required amount of salt solution is then added at once.

General Review

EXPERIMENTAL TAR CANCER*

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NEW YORK

(Continued from page 576)

THE TAR TUMOR

Inception of Malignancy.—The difficulties and uncertainties of morphologic diagnosis make it impossible to decide just when malignancy sets in. The long series of frequently repeated tar injections that Russell [240] found were required for the production of sarcoma led him to suggest that a slow cycle of changes in the cells of the reacting tissues must be gone through before the neoplastic change supervenes. The connective tissue surrounding the masses of tar was the seat of a fibroblastic reaction, which was more vigorous in the rat than in the mouse; yet even after several months of weekly injections the connective tissue of the rat about old tar masses was in an apparently quiescent condition. Nothing to suggest an alteration in this reaction, nothing that could be interpreted as a benign growth, was discoverable, and it appeared to Russell that the microscopic observations pointed to a sudden onset of the neoplastic change, as though nature had departed from the common rule and had proceeded per saltum.

Itchikawa and Baum [114] have suggested that carcinoma in the rabbit may also be the result of a sudden transformation to the malignant state, though like other investigators they emphasized the impossibility of deciding at what precise moment the change is initiated.

Carcinoma.—In both the rabbit and the mouse the malignant tar tumor is almost always a squamous cell carcinoma. In the rabbit, Yamagiwa and Itchikawa [279] found that the great majority of cancers belonged to the rodent ulcer type, although occasionally they encountered one resembling the trichocarcinoma of man, or one that seemed to have arisen in the sebaceous glands.

Itchikawa and Baum [113] have proposed the following classification of tar lesions in the rabbit:

I. Diffuse epithelial hyperplasia and hypertrophy.
II. Localized epithelial hyperplasia.
  (*a*) Benign folliculo-epithelioma (papilloma).
  (*b*) Benign sebaceous adeno-epithelioma (sebaceous adenoma).

*From the Institute of Cancer Research, Columbia University, F. C. Wood, Director.

III. (*a*) Malignant folliculo-epithelioma (malpighian carcinoma or epithelioma)
1. Preliminary stage.
2. Impending stage.
(*b*) Malignant sebaceous adeno-epithelioma (sebaceous carcinoma or epithelioma).
1. Preliminary stage.
2. Impending stage.

IV. (*a*) Malignant folliculo-epithelioma (definite malpighian carcinoma or epithelioma).
(*b*) Malignant sebaceous adeno-epithelioma (definite sebaceous carcinoma or epithelioma).

All these terms are self-explanatory except "preliminary stage" and "impending stage." In the former the epithelial cells commence their emancipation and, assuming a stellar or fusiform shape, arrange themselves in a network. The first signs of pearl formation appear, and invasion of lymph-vessels and lymph-spaces begins.

In the impending stage these characteristics grow more and more distinct, particularly emancipation and the formation of a network. Mitoses become more numerous, and the epithelium penetrates as far down as the cartilage of the ear.

In the fourth stage, definite carcinoma, Itchikawa and Baum [114] have described penetration through the cartilage, ulceration, keratinization, and variations in shape, size and staining qualities of the invading cells.

The tar cancer of the mouse needs no extended description, since it resembles that of the rabbit. As Murray and Woglom [199] have remarked, it presents all the varieties of histologic structure encountered in squamous cell carcinoma occurring naturally in man and the lower animals.

These authors found that tumors which arise after prolonged tarring are often less differentiated than those developing after a shorter interval of irritation. The earlier carcinomas in their series showed practically normal differentiation, with an abundant or even excessive formation of keratin, and maintained this feature after transplantation, whether into the mouse itself or into other mice. Later tumors, on the other hand, were likely to be less differentiated, with little keratinization and prickle cells badly formed or absent. While this distinction was not absolute, it appeared often to be true that the longer it takes to set up the malignant change the more atypical will the growths tend to be.

The cytology of tar tumors, with special reference to the mitochondria and the Golgi apparatus, forms the subject of a recent paper by Ludford.[168a]

The spontaneous healing of tar carcinoma has been studied in the rabbit by Yamagiwa and Itchikawa [277, 279] and more recently by Itchikawa and Baum.[114] Cure takes place more often in tumors which have not advanced beyond the stage of impending cancer, although some instances

of regression of a definite carcinoma have been encountered. Spontaneous healing is ascribed to a vigorous connective tissue reaction, which stops invasion and destroys the cancer cells by compression.

This reaction has been investigated in both the rabbit and the mouse by Roussy, Leroux, and Peyre,[233, 237] who compared it with the areas of local healing in man, and dismissed it with the conclusion that it was interesting but inefficient.

Sarcoma.—The occurrence of sarcoma after the injection of tar has already been discussed, but several authors have described the development, after tar painting, of what may for the present be called sarcoma. Itchikawa and Baum [114] mentioned three instances of spindle cell tumors on the rabbit's ear, which they prefer to call spindle cell epithelioma—the only cases that have been reported in this species so far as I am aware.

Sarcoma has been more frequently recorded in the mouse than in the rabbit, perhaps because a larger number of tar-painted mice have come under observation. The first case in either species was that of Tsutsui,[262] which occurred in the mouse and is referred to in the brief report of his paper simply as a tumor with the structure of a spindle cell sarcoma.

Fibiger [83] and Fibiger and Bang [88, 89] saw two carcinosarcomas. One proved to be transplantable, and it may be of some significance that the sarcomatous portion finally overgrew the carcinomatous, an event which has been observed frequently in the ordinary transplantable carcinosarcoma of the mouse.

Bang [4] subsequently published a series of 115 tar carcinomas of the mouse, five of which contained areas of spindle cell sarcoma.

Fibiger [87] has recently reaffirmed his belief in the sarcomatous nature of these spindle cell tumors, pointing out that the tumor which he and Bang transplanted had now been propagated for thirty-one generations during three years, and that it had faithfully preserved the typical structure of a spindle cell sarcoma.

Bierich and Möller [24] held a similar opinion, saying that they had proved their carcinosarcomas to be true mixed tumors by separating the two constituents and cultivating them separately.

The difficulty of deciding without transplantation is well shown by the experience of Murray and Woglom.[199] In their series of tar tumors of the mouse there were three which might have been either spindle cell carcinomas or carcinosarcomas. Unfortunately, only one proved to be transplantable; its daughter tumors were all squamous cell carcinomas, with slightly developed keratinization and no suggestion of a sarcomatous nature.

Deelman [63, 66] discovered areas with a sarcomatous structure in several of his ulcerating tar carcinomas and one ulcerating, pure sarcoma. None of his carcinomas were transplantable, but the sarcomas always

grew, and one had reached the sixteenth generation when his paper appeared, preserving its sarcomatous structure without the slightest change. His illustrations, and the fact that these spindle cell neoplasms grew so well, make it hard to believe that they were not actually sarcomas.

Roussy and Leroux [231, 232] and Roussy, Leroux and Peyre [233] have given special attention to the question of these puzzling spindle cell tumors. They were convinced that such neoplasms are actually carcinomas, and said that they had succeeded in discovering an epithelial pearl in the "sarcomatous" portion of one of Fibiger's carcinosarcomas. Their reasons for deriving these growths from the epithelium may be presented in abridged form as follows:

1. Transitions between spindle cells and undoubted epithelium can readily be found.
2. A tar tumor in which the spindle cell predominates may give rise to metastases containing keratin.
3. A tar tumor in which keratinizing epithelium predominates may give rise to both keratinizing and pure spindle cell metastases.

E. Möller [189] observed a tumor with cells resembling those of a sarcoma, and cited a similar observation by Dreifuss. She called her tumor a carcinoma of sarcoma-like growth, and said that epithelial pearls were entirely lacking. For this reason she referred its origin to the basal cell layer, and suggested that it might be regarded as a basal cell carcinoma were it not that the basal cell carcinoma, of man at any rate, is relatively benign, whereas this tumor of the mouse grew vigorously on transplantation into other mice.

Lipschütz [165] gave an account of two spindle cell tumors in tarred mice, the sarcomatous nature of which was demonstrated by the van Gieson, Mallory, and Bielschowsky methods, and Maisin [171] referred briefly to two carcinomas that had been found among his tar tumors. While not desirous of taking either side in the argument, Maisin remarked in passing that he had been unable to discover any epithelial pearls in the spindle cell portions of these growths.

Mandl and Stöhr [176] mentioned a sarcoma developing at the site where a tar ulcer had been extirpated, but gave no description of the neoplasm.

Truffi's tumors [259, 261] included a sarcoma and a carcinosarcoma. In the latter he could discover no indication that the spindle cells were of epithelial origin.

On the basis of unpublished experiments by Azuma, Yamagiwa has suggested that many of the so-called tar sarcomas in mice may have been carcinomas. Azuma's neoplasms contained no epithelial pearls, but this might be accounted for by assuming that the epithelium had been so strongly stimulated that there had been no time for it to differentiate.

It is evident that these spindle cell tar tumors of the mouse are in the uncertain position occupied by the spindle cell neoplasm which arises in the same species in connection with spontaneous and transplantable carcinomas, and which is regarded by some investigators as sarcoma and by others as spindle cell carcinoma. The evidence for both sides has been fully reviewed by Ewin [82a] and by Woglom,[269a-c] to whose articles the reader is referred.

Melanoma.—Multiple melanomas have been observed by Lipchütz [159-164] in tar-painted gray mice, but not in albinos. These appeared from twelve to sixteen weeks after tarring had been begun, first in the vicinity of the painted area and later at a distance. No relationship was discoverable between their development and exposure of the mice to light.

Three stages of pigmentation were distinguished by Lipschütz:

1. Pigmented pachydermia, in which the thickened skin is of a rather uniform dark gray to grayish-black color, and later presents a more mottled appearance.

2. Macular melanomas. These are sharply circumscribed, deep black spots up to 2 mm. in diameter.

3. Nodular melanoma. This rare lesion is distinctly elevated above the surface of the skin.

Lipschütz referred the pigmentation to chronic tar poisoning, which stimulated the ferment action underlying pigment formation in the skin.

Pigmentation occurs also in the human subject after exposure to tar, and has been ascribed by Kissmeyer [139] to the cause proposed by Lipschütz.

The melanomas of tar-painted mice have received practically no notice from other investigators. Handl and Stöhr [176] reported the discovery, in the skin of white mice, of cells morphologically similar to those found by Lipschütz in the melanomas of deeply pigmented mice. Yamagiwa [271] thought it strange that not a case of melanoma had occurred in Japan, leaving out of account the little collections of melanoblasts which, like mast cells or plasma cells, probably represented a reaction of some sort to the irritant.

Mast Cell Tumor.—A unique tumor has been recorded by Schreuss.[244] This was a twenty day old nodule, in a white mouse that had been painted for three and a half months with a neutral tar oil having a boiling point of from 200 to 380 C. It arose in close proximity to one of the characteristic papillomas, and on microscopic examination proved to be composed entirely of mast cells.

Transplantation.—The transplantation of tar cancers was attempted by Yamagiwa and Itchikawa [274] early in the course of their experiments, but neither autoplasts nor homoplasts were successful. In a later communication, however, Itchikawa [109] reported the propagation of a cancroid of the rabbit's ear for three generations.

There are two reasons for the difficulty often encountered in getting tar cancers to grow after transplantation. They are nearly always ulcerated, and therefore infected; and they are almost uniformly of the keratinizing type, a neoplasm which long experience prior to the era of tar cancer had shown to be almost entirely refractory to propagation.

Yet in spite of this, tar cancers of the mouse have been propagated. Thus Kashiwagi was said by Yamagiwa [271] to have transplanted a dancing-mouse carcinoma for one generation. Fibiger and Bang [88, 89] reported the transfer of a carcinosarcoma and two carcinomas; Borrel, Boez, and de Coulon [39] also transplanted two carcinomas; and Murray and Woglom [199] succeeded with both autoplastic and homoplastic transplantation.

Bierich and Möller [24] reported that they had twice been successful in propagating metastases, and in Bierich's experience [20] the transplantation of tar tumors had not proved difficult, although they usually died out after two or three generations; in one instance, however, a growth had been transplanted, at the time of writing, through thirteen.

Deelman,[63, 66] like Jordan,[122] failed to transplant tar carcinomas of the mouse, although he had succeeded with sarcomas. Grafts from carcinomas broke down into abscesses, whereas those from sarcomas which were badly ulcerated, and therefore presumably as heavily infected, proliferated vigorously. Deelman suggested that this might indicate a higher growth power among the sarcomas.

It appears to me that this is the correct explanation, as it has been known for years that the transplantable sarcomas of the mouse grow more vigorously than the carcinomas—so much more vigorously that an immunity which will prevent the establishment of a carcinoma will be quite powerless against a sarcoma. And it seems to me, too, that this greater proliferative energy is the best of proofs that many of the spindle cell tar tumors are actually sarcomas, and not spindle cell carcinomas.

Particular attention has been paid by Roussy, Leroux, and Peyre [239] to the relation between infection and transplantability. Seventeen tumors proved by microscospic examination to be carcinomas were transplanted into eighty-one mice, the grafts being taken from the edge of the tumor, and at some depth, in order to exclude necrotic and infected areas. Only one of the seventeen was transplantable, and this gave but one tumor in the seven mice inoculated; a second generation, transplanted into three mice, failed entirely. As almost all the tumors of this series were ulcerated, rich in microbes, and sometimes even contained pus, the authors thought that infection might explain some of the failures; but they did not believe that it would explain all, for histologic signs of inflammation in the tumors themselves or in the tissues of the hosts immediately surrounding their grafts, were only

exceptionally seen. They concluded that tar cancers are less easily transplantable than the common spontaneous mammary carcinomas of the mouse.

It will not have escaped the reader, however, that fewer mice were used for seventeen tar tumors than are generally employed for one spontaneous neoplasm. Indeed, before spontaneous mouse tumors were so common as they are today, and at a time when it was essential to make the most of every one, it was considered necessary to inoculate 400 or 500 mice with each one that it was desired to cultivate. And the investigator who obtained half a dozen progressively growing tumors for his pains counted himself fortunate. In the second generation it was customary to inoculate several hundred animals, and so on, until finally the tumor was established.

It is to be hoped, therefore, that Roussy and his colleagues will repeat their observations on a large series of mice, since their suggestion of the lower malignancy of tar tumors coincides so well with the frequent regression of tar tumors in both animals and man that it would be interesting to have it confirmed by a supplementary experiment.

Metastasis.—Every one who has worked with tar tumors agrees that they metastasize readily to the lungs or the lymph-nodes, and occasionally to other organs. The manner in which they spread has been studied in particular by Begg,[15] on a material consisting of 140 tumors. Invasion of the lymph-channels was observed in many of his cases, although only four showed metastases in the nodes. Widespread involvement of the lungs, on the other hand, was a common finding, and in one of these cases, in which the hilum was cut in serial section, many of the blood vessels were occluded or extensively involved. Invasion of the nerves, although a form of lymphatic invasion, was considered separately by Begg for facility of description. It occurred with surprising frequency, no less than 26 of the 140 cases examined showing it, that is, 18.5 per cent. The usual appearance was a collar of tumor cells completely surrounding the nerve, or only a crescentic mass of cells at one side, but a more diffuse invasion by single cells or small cell groups was a common occurrence. This diffuse dissemination occurred most typically when the primary growth contained a large number of polymorphic cells in addition to the usual squamous ones, a feature which suggested that these polymorphic elements were more actively ameboid and thus better able to insinuate themselves among the nerve fibers once the perineurism had been penetrated.

Begg pointed out that the invasion of nerves by spontaneous mammary tumors of the mouse had been described by neither Murray nor Haaland, although both had had unrivaled experience with these growths, and concluded that when the cutaneous epithelium of the mouse has become cancerous, it shows a tendency to invade the nerve stems, which

is in marked contrast to the absence of such invasion by mammary epithelium which has been similarly changed.

Nerves in Tar Tumors.—As Engel [82] had suggested that the narcotic action of certain constituents of tar may paralyze the regulatory action of the cutaneous nerves, thus allowing the outbreak of carcinoma, Itchikawa, Baum, and Uwatoko [117] began a series of observations on the tar tumors of rabbits and mice. Their studies showed them that the newly formed blood capillaries and lymph-channels in the stroma contain young nerve fibrils, that other fibrils develop in certain portions of the tumor, and that there is no degeneration of nerves except when they become involved by invasion of the neoplasm. Thus the stroma undergoes a gradual augmentation in the number of its nerve fibrils.

In a subsequent paper, Itchikawa and Uwatoko [119] confirmed the presence of peripheral nerves in tar tumors of the mouse and rat and, the following year,[120] in benign and malignant neoplasms of the human subject.

In the discussion of these observations, which is appended to the third paper,[120] Berger expressed the opinion that some of the structures regarded by the authors as nerves were really elastic fibers, while Mawas was not convinced that all of them were nerve fibrils. Roussy and Lhermitte, on the contrary, thought that the preparations demonstrated the presence of nerves in tumors, and Leroux and Delbet said that, as the question was one of staining specificity, it was not susceptible of solution at present.

On his recent visit to New York, Dr. Itchikawa was so kind as to show me his preparations, and we sought together the opinion of several of the foremost neuro-anatomists in the city. While none would say positively that the fibrils in question were not nerves, none would agree that they were; the general feeling seemed to be that they were not nerve fibrils.

At present, therefore, it can be said only that Itchikawa has undertaken a problem which is of extreme difficulty, and which may even be insoluble with the means now at our command.

Nakamoto [199a] has recently described the degeneration of nerves within a tarred area after from twenty to forty days of painting, expressing his disagreement with Itchikawa and his belief that malignant tumors develop independently of the nervous system.

This subject will be discussed from another aspect in a subsequent paragraph.

ETIOLOGY

Local or Constitutional Action of Tar in Etiology.—There are almost as many explanations of the way in which tar produces a malignant growth as there are investigators. The principal argument has centered,

however, about the question whether its action is purely local, or whether it brings about a constitutional change of which cancer is but the local manifestation.

The reason underlying the latter view is the observation that tumors may arise at a distance from the tarred area. One of the first to record this was Maisin,[171] who found carcinomas or papillomas in mice on the lower jaw, the side of the thorax or on the back outside of the painted region. Mertens [186] has recorded similar instances in the same species, ascribing them to a constitutional action by the tar, as has Truffi,[259, 261] who, on the contrary, attributed them to tar accidentally transferred.

Among the mice of Burckhardt and Müller,[44] which were painted at the root of the tail, there was found one with a tumor of the snout. The authors ascribed this distant tumor to tar that had been transferred from the painted area, but Mertens objected to this explanation on the ground that he had never seen a mouse cleanse itself of tar by licking it off and that tar was, in fact, obviously repulsive to them.

On account of the conflicting opinions respecting the simple question whether or not animals will remove tar with the mouth, I have tarred rats and mice at various sites and watched them attentively afterward. And I have seen a mouse with a tarred forepaw take the paw in its mouth several times in the course of an hour and endeavor to remove the tar with its teeth. A rat tarred at the nape of the neck swept the forepaws over the irritated region and then licked them off, and licked and bit at a patch of tar that was matting together the hair on the flank. In both species, attempts were made to remove tar from the back of the neck by scratching at it with the hind paws, which soon became obviously soiled with tar. It was clear that the tar offended both smell and taste, yet nevertheless these rats and mice used their mouths in making their toilet, and, furthermore, certainly transferred tar to other regions outside the painted area.

In discussing his own experience, Lipschütz [166] said that he did not think distant tumors could be referred to tar transported during attempts of the mouse to clean itself, because it is necessary to apply the irritant for months and to elicit a profound change in the skin before carcinoma develops.

In a group of twenty-four rats tarred by P. Möller,[190] all six that survived for 300 days had squamous cell carcinoma of the lung. But he did not think that this observation supported the view that tar may act at a distance, since these tumors might have been due to the local effects of tar particles that had been inhaled, or to tar that had been absorbed, and later excreted by the lungs.

Krotkina [144] noted a cancer near the base of the ear in a rabbit, well outside the tarred area. She was unable to decide, however, whether it

was a result of the transportation of tar along the lymphatics, of constitutional action or of transfer by the animal's paws in scratching.

Buschke and Langer [48] found that the introduction of tar into the rat's rectum was entirely unsuccessful so far as the production of a tumor at that site was concerned. But in nearly all the animals that lived long enough there appeared papillomatous or ulcerative lesions, limited to the forestomach, which macroscopically resembled those elicited by *Spiroptera* in the experiments of Fibiger. Microscopic examination showed the presence of inflammatory hyperkeratosis, the absence of nematodes, and no lymph-node invasion. Scharlach R produced no such changes, nor were they demonstrable in other rats. The authors anticipated any objection that tar might have been licked off and swallowed by the assertion that they had never seen a rat cleanse itself of tar in this way, and that rats would neither touch food that had been contaminated with traces of tar nor approach tar-soaked rags hung in their cages.

Pappenheimer and Larrimore,[203] however, have described ulcerative and papillary lesions in the esophageal portion of the stomach in a large proportion of rats maintained on an insufficient diet, which were rarely present, if ever, when the diet was adequate. These changes, in the causation of which ingested hairs played an important part, were so frequently found that the authors believed they must be taken into account in any experimental work on the rat.

Continuing his first observations, which had led him to the conclusion that tar must exert some generalized action, Maisin [172] painted one lot of mice for two months on the nape of the neck and then suspended the applications; a second group was tarred in the same way for two months, and then for two months longer at the base of the tail only. At the end of 180 days, one of ten survivors (10 per cent) in the first group had carcinoma and two had simple papillomas; in the second lot, five of seven (71 per cent) had developed carcinoma, and one that died after five months had a papilloma. All the cancers had originated toward the center of the area first painted (nape of the neck), except in one animal which had a cancer in both tarred regions.

Maisin interpreted this to mean that when painting was continued at another site the effect produced in the first area was continued; in other words, that the action of tar was not local but general. This would explain the occurrence of tumors in nontarred areas in his own experiments and in those of others; for even though tar actually was spread by the animals as they made their toilet, the quantity thus applied was too small, and the time during which it remained too short, to produce cancer.

Maisin and De Smedt [173a] painted one lot of mice three times a week for two months, and in a second lot applied the same number of tarrings

but extended them over four months. Among nine survivors in the first group, only two had cancer at the 310th day; the other seven had not even developed papillomas. But all seven survivors in the second series were dead of cancer on this day, an observation which the authors explained by assuming that although the same amount of tar had been applied, there had been time for more of it to be absorbed.

Maisin and Masse [174] approached the problem in still another way. A drop of tar was injected every two weeks under the skin of the abdominal wall for four months. The mice were then painted on the nape of the neck for two and a half months, three times weekly. After 130 days, ten of twelve (86 per cent) had cancer, whereas among non-injected controls, painted in the same way, two out of twelve (17 per cent) had developed it.

Again the authors concluded that, in addition to its local action, tar has a general toxic effect of such nature that the poisoned organism responds more readily than the normal body to a carcinogenic agent.

Cramer [60] said that among the large number of mice which had been tarred at the Imperial Cancer Research Fund, only three had developed tumors outside the area actually painted; and that even in these three exceptional cases the growth had appeared in the immediate neighborhood of the tarred region, following in two of the mice an incision of the skin around the painted zone. He thought it probable that in these three instances either the chronic irritation induced by the tar had spread a little beyond the painted area, or the animals by scratching had transferred some of the tar. Cramer pointed out that a strictly localized response had been noted by most other observers as well, the experience being so general as to suggest that the genesis of cancer is exclusively a local process in which only the cells subjected to chronic irritation are concerned, without the intervention of systemic factors.

He recalled the experiments of Leitch, in which an area of skin painted for a time and then left alone had developed tumors, as well as Findley's observation that a single application of tar may excite malignant growth; and he suggested that Maisin's experiment [172] was open to the objection that the preliminary course of tar painting had in itself been sufficient for carcinogenesis.

In order to test the possibility that the absorption of tar may diminish the general resistance, Cramer carried out the following experiment. Mice were painted on the back of the neck for six months, but only once a week, the object being to allow the absorption of tar over as long a period as possible without eliciting a tumor. The tarred zone was then widely excised and examined microscopically; in no case had a tumor been produced. The neighboring skin over the left shoulder was now painted twice weekly. If the preliminary treatment with tar over six months had diminished the resistance to carcinogenesis, tar tumors should

have appeared on the left shoulder of these mice before they did in a control batch of mice tarred at the same time. This was not the case, however.

A similar unpublished experiment by Murray was cited, in which analogous results had been obtained.

Cramer concluded that his own experiments did not suggest the occurrence of a constitutional change favoring carcinogenesis as a result of the absorption of tar, but he thought that the paper of Maisin and Masse, which had appeared after his own work had been completed, contained somewhat more conclusive evidence of such an alteration than the earlier paper of Maisin which he had been discussing.

Itchikawa and Baum,[111] on the other hand, were of the opinion that in order to incite carcinoma in the rabbit it was necessary to produce a general intoxication. And Itchikawa [110] himself has explained that as long as the animal tolerated the tar and continued in good health, only folliculo-epithelioma or the first stage of cancer would arise; continuation of the tarring in a healthy animal would lead, as a rule, to spontaneous cure, or at most the tumor would not progress, whereas the occurrence of prostration and anorexia was almost universally followed by the development of a metastasizing carcinoma.

During the precancerous stage in tar-painted rabbits, Rémond, Sendrail, and Lasselle [224] found that the p_H of the plasma was low (7.16 to 7.27), and by the time that carcinoma developed it had become so low as to constitute a true acidosis (7.06 to 7.27). It never returned to normal unless the tumor regressed (7.35). The p_H in their eight rabbits before painting was begun ranged from 7.21 to 7.43.

The alkaline reserve did not vary so regularly, but it generally rose with the approach of malignancy and fell later, so that the stage of full malignancy was characterized by a "decompensated" acidosis. By this term it may be presumed that the authors mean that condition referred to in this country as uncompensated acidosis, in which the respiratory center does not respond promptly enough to prevent a fall in the p_H of the blood. The fatty acid content of the blood demonstrated by their previously published analyses [223] was regarded by Rémond and his collaborators as a satisfactory explanation of this acidosis.

Ionized calcium was low when cancerization set in, but might rise later.

The authors therefore regarded cancer as a general rather than as a local disease.

I do not understand, however, why these blood changes cannot be ascribed solely to tar intoxication, a condition which might so easily coexist with tar cancer and yet play no part in its etiology. Furthermore, the number of rabbits in these experiments was small; thus, the drop in p_H was observed in two groups, containing respectively four and three

animals, and the statement that the p_H returned to normal if the tumor regressed was based on one rabbit.

In a previous paper these authors [223] recorded a lowering of urea nitrogen and a rise in residual nitrogen, which they referred to the action of tar on the liver. Hyperglycemia and hypercholesterinemia appeared with the first histologic evidences of malignancy as a result of the noxious activities of the cancer cell.

In the discussion of this paper, Roussy pointed out that the differences in the figures were small, and that only six rabbits had been employed. In any case, he thought that the hyperglycemia and the hypercholesterinemia might have been due to the tarring.

The wide distribution of the melanomas described in a preceding paragraph led Lipschütz [166] also to the conclusion that carcinoma is not a local disease, but the localized expression of a general toxicosis.

Bonne [35] had noticed that a certain number of tarred mice developed papillomas of the mouth and stomach, comparable in every respect with tar papillomas of the skin, if they survived for from nine to twelve months. Some of his best examples occurred in mice that had not been painted themselves, but that had been kept in the same jar with one that was being tarred; such mice ingested tar with their food, or in consequence of licking themselves, and the amount thus taken in might be considerable in the course of a year. In such cases, the papillomas of the stomach arose after a latent period that was much longer than that for painted mice. He also recorded papillomas about the mouth in four rabbits whose backs or ears were being tarred.

In view of the experiments of Maisin and Masse, Bonne thought it possible that these papillomas might be the consequence of a constitutional action by the tar, but he did not believe that a purely local action could be excluded.

Bonne and Stoel,[38] in the following year, recorded the discovery of adenocarcinomas in the lungs of mice that had been tarred, and even of those merely kept in a jar with one that was being painted. In painted mice they had observed, also, cancer of the vault of the pharynx and of the esophagus.

If their mice were painted twice a week until cancer developed in the skin, this appeared after about four and a half months of tarring. When the mice died from four to six weeks later, the internal organs rarely contained tumors that were not metastatic, although now and then adenocarcinomas were found in the lungs. If tarring was discontinued, however, before the appearance of tumors in the skin, cancer arose in the tarred area after a latent period longer than four and a half months, and it was in these animals that adenocarcinomas of the lung, and the papillomas of the gastro-intestinal tract previously reported by Bonne, had been found.

Murphy and Sturm [194] have given special attention to the lung tumors of tarred mice, and have devised a technic to eliminate the possibility that these are metastatic. They applied tar to different areas on the skin, in such a way that no single region was irritated for a sufficient length of time to produce a carcinoma there. Mice thus tarred showed a high incidence (60 to 78 per cent) of epithelial tumors of the lung, whereas the maximum for the controls was but 5 per cent.

Obviously the pulmonary neoplasms were not metastases, and the authors therefore suggested that tar might so alter the bodily state that tumors would arise at points of incidental irritation, such as might follow the inhalation of particles from the sawdust and hay in which the mice burrow, where they would not develop under ordinary circumstances.

In respect to the microscopic character of these growths, the authors said that the cells comprising them were of a fairly large size and cuboidal or ovoid in shape, and that they usually lay in a single layer on either side of a thin shred of stroma. Mitotic figures were present in fair number. As a rule the tumors were sharply demarcated from the lung, although it was not uncommon to find finger-like processes invading the surrounding tissue. They were identical in structure with those described as primary tumors of the mouse lung by Livingood, Haaland, Tyzzer, and Murray, and variously designated as adenocarcinoma, papillary cyst-adenoma, and adenoma. Judging from the published descriptions and illustrations, the authors thought that there was but little variation among them, and that they unquestionably represent a distinct type of epithelial new growth.

Finally, Yamagiwa, Fukuda, Kaneko, and Azuma [288] have found that the same length of time may be required for tar carcinoma to develop when the opposite ear is painted as was required in the first instance, an observation which led them to the conclusion that a general intoxication by tar can hardly be a prerequisite for the development of cancer.

Soil.—Views on the relative importance of soil and irritant range from that of Bloch,[30] who produced carcinoma with a certain sample of tar in all strains of mice painted with it and who therefore believes that the irritant is of more significance than the tissues, to that of Roussy [230] and his collaborators, Leroux and Peyre,[233] who ascribed great importance to the soil. But there is probably no one who would implicate one of these two factors to the entire exclusion of the other, and the great majority occupy the safe position taken by Mertens,[184] who believes both to be of weight, though some seem inclined to emphasize one factor and some the other.

Thus both Loeb [167] and Miss Slye [281] think that if an irritant is strong enough it may overwhelm and conceal any inherited resistance to the development of cancer.

Deelman [68] painted mice with two varieties of tar, and noticed that the length of time required for the development of cancer was the same in each case, no matter what breeds of mice were employed. He therefore expressed the belief that discrepancies in the yield of tumors reported from various laboratories were probably due to differences in the tars employed, rather than to variations among the animals.

Lubarsch [168] has remarked that the high percentage of success obtainable in certain species, and in any part of the body, shows that neither individual nor local predisposition plays the chief rôle in the genesis of cancer; and that it confirms the opinion, which he has long supported, that cancer depends, not on the kind of irritation, but on its intensity and the length of time during which it operates. There still remained the question, however, in the case of both human and animal tumors why, under the same conditions, one develops cancer early, another late and a third not at all. This he believed to be a matter of constitutional predisposition.

With this view Teutschlaender [256] could not entirely agree, for certain parasites produced cancer and others did not; arsenic but not other elements. As for tar, it might be said to have a relative specificity, since it causes inflammation, benign growths or malignant growths. Three factors seem to be necessary for malignant proliferation: adequate exposure, a relatively specific agent and predisposition.

Borrel, Boez, and de Coulon [39] pointed out that only the rabbit's and the mouse's skin react to tar, that the resulting tumors might vary in type, or that none might appear. This they believed could hardly be explained by assuming that neoplasms were the result solely of some physical or chemical activity; while as for soil, invoked by some authors to explain these differences, it was but a word after all. Borrel and his colleagues therefore suggested that these variations in the consequences of tarring might correspond with the presence or absence of parasites, such as the nematode worm which the senior author had shown to be so often associated with mammary carcinoma in the mouse; they said that they had, in fact, found nematodes in some of their cases of tar cancer in mice.

The suggestion has been dismissed, however, by Itchikawa and Baum,[113] who reported that they had never been able to discover parasites of any kind in rabbits with tar cancer. Nor had Bonne [36] noticed any relationship between tar cancer and infestation with *Klossiella muris*.

Others who have attributed considerable importance to soil are Bang,[7] Parodi,[206] Fibiger [83] and Yamagiwa.[271] Champy and Vasiliu [55] have suggested that the failure of some mice to develop cancer was no proof of their resistance, for in a large part of the painted area neither papilloma nor carcinoma ever appeared. Thus the action of tar might vary

at different points, and it was not right to demand that all mice should present similar lesions as a result of painting.

Diet.—Certain investigators have endeavored to gain some information in respect to the importance of the soil as an etiologic agent, by modifying it in various ways or by observing its reaction in the face of a physiologic alteration such as pregnancy. Fibiger [83] asserted that diet had no effect on the development of tar cancer in mice, and in the following year an experiment was recorded by Passey [208] in which the effect of vitamin deficiency had been investigated. One group of fifty white mice was fed on a diet very rich in fat-soluble A, another on one in which that factor had been eliminated as completely as possible, and all were painted with a basic ether-soluble fraction obtained from chimney soot. At the end of the fifth month the only noticeable difference between the two lots was that warts appeared a little earlier in the animals maintained on the vitamin-poor regimen. There was no important difference in the number of malignant tumors produced (42 per cent in the vitamin-rich, and 47 per cent in the vitamin-poor group). The neoplasms all resembled those elicited with tar by other investigators, and did not vary appreciably in rate of growth. Malignancy was determined when possible by autoplasty; otherwise, by recurrence after wide excision, metastasis or deep invasion.

Roussy, Leroux and Peyre [233] also tried to modify the constitution of the soil by changes in the vitamin content of the diet or by administering magnesium, but their results were not yet conclusive when their paper appeared.

Mandl and Stöhr [176] obtained a strikingly small yield of tumors in comparison with Lipschütz, although they used the same tar which he had employed. They suggested that differences in diet might be responsible for this discrepancy, as their mice had been given bread with plenty of water, whereas those of Lipschütz had been fed almost entirely on legumes and had received no water.

Eber, Klinge, and Wacker [81] fed mice on a diet which it was hoped would stimulate epithelial growth. This consisted of a paste made of skimmed milk, flour and water, to which was added a fat in which cholesterol and scharlach R had been dissolved. As the aim of the experiment was to determine whether this diet favored the occurrence of tumors, an irritant was chosen that produced carcinoma in a low percentage of cases. According to Döderlein, a mixture of tar and crude paraffin oil is much less active than tar alone, and the authors therefore employed a mixture of tar with 20 per cent of this oil.

Twelve mice were fed on the special diet. Of the nine that appeared in the final reckoning, six had carcinoma; of nine controls kept on the ordinary laboratory diet, six came to final examination, of which two

had carcinoma and one a benign tumor. The criterion for the diagnosis of carcinoma was metastasis or, in its absence, invasion of muscle. Papillomas appeared in the mice maintained on the experimental diet after two months, and in the controls not until after five months. The authors thought that any stimulating action which their special diet may have had was to be ascribed to the cholesterol, but realized that the number of animals was too small to be of any value.

Borst [41, 42] found that in about 40 per cent of rabbits fed with cholesterol the tarred ear was more swollen and hot than in the controls, and that cancer developed sooner; in one instance it arose as early as four weeks after the first tarring.

Hydrous wool fat was added to the diet of tarred rabbits by Ri [226] and by Lee, Fukuda, and Kinoshita,[148] who found that it hastened the appearance of folliculo-epithelioma and accelerated its growth because the fatty changes in the connective tissue facilitated invasion by the epithelium. A similar observation has been published by Yamagiwa and Murayama.[285]

Pregnancy.—As for the effect of pregnancy, Parodi [206] reported that it had no influence on the development of tar cancer of the skin in mice; but when tar was injected into the breast of the rabbit, it seemed to Yamagiwa and Murayama [285] that carcinoma appeared more often in pregnant animals.

Castration or Splenectomy.—According to Maisin, Desmedt, and Jacqmin,[175b] castration of male mice did not prevent the development of tar tumors, although the authors were under the impression that papillomas in castrates became cancerous at an earlier period and that metastasis occurred with greater frequency than in controls. Experiments were under way with mice castrated before or after puberty.

Parodi [207] did not find that splenectomy, or the castration of males and females, exerted any influence on the growth of tar carcinoma in mice. Blocking of the reticulo-endothelial system with pyrrhol blue, on the other hand, seemed to slow down the development of cancer.

According to Maisin and Van de Vyver,[175a] the intradermal injection of emulsions of tar tumors during the period of painting had no effect on the development of neoplasms.

Insulin.—Münzner and Rupp [191] reported that they had obtained some evidence to suggest that insulin inhibited the growth of tar tumors in mice, but wished to continue their experiment before coming to a definite conclusion.

In rabbits, insulin delayed the appearance of papillomas in the preliminary experiment of von Witzleben.[265] When his paper appeared, however, twelve rabbits had been painted for only seven and a half weeks. The first warts developed in the controls after five weeks, while

in the animals given insulin the ears were still smooth after seven and a half weeks. In another group that received epinephrine and glucose, the first papillomas appeared in nineteen days in three quarters of the rabbits treated.

Rondoni [228a] has found that the injection of glucose into rabbits hastens the appearance and the development of tar papillomas.

Trauma.—Cramer [60] attempted to influence the soil by bringing about absorption of the animal's own cells, a process which he conceived might very well occur in chronic irritation. This he did by removing the spleen in a group of sixty-three mice, mincing it rapidly, and returning it at once to the abdominal cavity. After they had recovered from the operation, the mice were painted with tar twice a week, a control batch of fifty mice being tarred at the same time.

Among the mice operated on a considerable number of tumors appeared during the fourth month, although tumors never arose among the normal mice at the laboratory before the fifth, and only a very few then. At the end of the sixth month the splenectomized mice had nearly twice as many tumors as the controls, and not a few were of exceptionally rapid growth. As the spleen pulp regenerated in every one of the mice on which operation had been performed, absence of spleen could be excluded as a possible factor in his accelerated carcinogenesis.

Cramer concluded that systemic factors influence the origin of cancer, and that the experimental procedure adopted in his experiment had diminished the resistance of the mice to the genesis of malignant disease. But he did not think it possible to say with certainty whether the accelerated carcinogenesis was due as intended, to the absorption of damaged cells, or whether other and accidental factors were concerned in it.

This work of Cramer's recalls Deelman's scarification experiments and his observation of the development of tar tumors in eight mice at the edge of large healing wounds,[70] no less than the instances recorded by Lipschütz [165] and by Mandl and Stöhr,[176] in which malignant tumors promptly developed after excision of part of a tarred area. It brings to mind, also, the suggestion of Murray and Woglom [199] and its later elaboration by Murray,[197b] that the neoplastic change is not an immediate response to tar, but produced indirectly by secondary changes throughout the stimulated region.

Influence of a Preexisting Tumor.—In connection with the soil and its suitability for carcinogenesis, a puzzling phenomenon has been encountered by Murray, who first called attention to it in 1921.[195] He observed that in a group of tarred mice no mammary tumors had developed, which

seemed curious when one remembered the frequency of spontaneous carcinoma of the mouse mamma.

In the following year, he[196] reported that mice in which one tar cancer had developed had been tarred at another site, but that no second carcinoma had been observed, although in several instances the applications had been continued for longer periods than had been required to produce the first tumor. Furthermore, mice which had developed spontaneous mammary carcinoma had been operated on, and subsequently tarred for long periods without success. The two experiments seemed to indicate that the previous existence of a cancerous growth may in some way hinder the development of a second one.

Attempts to produce a second tar carcinoma are likely to be abortive, for experiments of this kind often end prematurely by the death of the animal from intercurrent disease or by reason of metastasis to the viscera from the first tumor. Therefore even after two years, and in more than fifty mice in which experimental tar cancer had been produced, the number in which the second tarring was at all commensurate in duration with the first was still very small.[197a-b] Murray gave in tabular form, as follows, the duration of the first tarring, the interval between the two series of applications, and the duration of the second tarring:

Identification Number	Duration of First Tarring	Interval	Duration of Second Tarring
1577	25 weeks	36 weeks	24 weeks
1632	58 weeks	8 weeks	25 weeks
1717	28 weeks	12 weeks	29 weeks

In none of these mice was there any indication of proliferative changes at the second site. The hair fell out in the treated area, and the skin was found to be atrophic when it was examined in sections. Murray regarded these observations, taken by themselves, as without significance, except incidentally for the doubt thrown on the assumed predisposing effect of age.

However, the result of a similar trial in mice with spontaneous mammary cancer increased the probability that these negative results were not fortuitous, but due to a real insusceptibility of the animals to the carcinogenic action of tar. In this experiment spontaneous mammary carcinomas were removed from fourteen mice, and the animals were then tarred for periods ranging from eight to thirty-seven weeks, only three, however, being painted for less than sixteen weeks. In six, scarification was combined with tarring for the whole or part of the time, yet in only one of these fourteen animals did a tar tumor of any sort develop; this was a papilloma which grew progressively after irritation had been discontinued, and its appearance in a mouse that had been tarred for but

eight weeks was regarded by Murray as an indication that the failure to produce any proliferative changes had not been due to insufficient duration or intensity of the applications. The exemption of all the others indicated a real inability to respond to a stimulus which would be carcinogenic for normal mice.

Another experiment was instituted to determine by how long a time the first stimulation must precede the second in order to prevent the development of cancer from the latter. Fifty mice were painted twice weekly on the left shoulder, and seven weeks after the first of these applications, tarring was begun in the right flank.

In two of the nine survivors carcinomas arose at both sites almost simultaneously; in four no growth occurred at the second site, although in all but one which died early in the experiment tarring had been kept up for a period as long as, or longer than, was necessary in the first instance; in three mice, the tumor which appeared at the second site was retarded in its development.

The nature of this secondary resistance to the induction of cancer Murray could not explain, although he pointed out that it was not a resistance to growth; otherwise metastasis could not take place nor could tumors be inoculated into their bearers. Again, it had nothing in common with acquired resistance to the growth of transplantable tumors, for both spontaneous neoplasms and tar carcinomas had been known to arise in immune mice. Its greatest interest and importance lay in its suggestion of a constitutional change in cancer bearers, which, if it could be recognized with certainty and rapidity, would enable us to discover cancer in its earliest stages; and which, could it be reproduced without initiating malignant disease, would place in our hands a rational means of prevention.

In his most recent paper, Murray [198] reported that if a second tarring were begun before cancer had developed from the first painting, a second carcinoma could be produced in nearly every case and in a time shorter than was necessary in the first instance. Thus at about the time when the first tumor arose, the whole animal seemed to be in a state of greater susceptibility to the carcinogenic action of tar.

Experiments like those of Murray require so much time for their completion that only four writers have so far been able to compare their experience with his; and once again it has to be recorded that opinions differ radically from one another. Parodi,[206] Truffi,[259, 261] and Lynch [170] have all encountered a second tar cancer, or a spontaneous neoplasm in a mouse bearing a tar cancer, or a tar carcinoma in a mouse from which a spontaneous mammary carcinoma had been removed; and Truffi said that not only may a mouse develop a second tar tumor, but that the time required for this to arise was notably shortened.

Miss Lynch found that the percentage incidence of tar tumors in mice from which spontaneous mammary carcinomas had been extirpated was similar to that encountered in the controls, except perhaps in the case of such animals as had suffered a recurrence of the mammary growth; in them the development of tar tumors seemed to be delayed and possibly prevented, but the number of mice in her experiment was too small to permit a definite conclusion.

Thus she thought that her work only partially confirmed Murray's observations, for if any opposition existed to the development of tar cancer after the ablation of a spontaneous new growth, it was only when recurrence had taken place. Still, the two experiments were not strictly comparable, for tar had been applied twice weekly to Murray's mice and three times a week to her own.

The problem which Murray's investigation presents is of the highest importance, though extremely difficult of solution, and no one would undertake to say at this time how widely it would be safe to generalize. Yet the comparison of tar cancer with spontaneous neoplasms is always interesting, however unjustified it may later prove to be, and the following observation is therefore presented for what it is worth. Among the first 211 mice with multiple spontaneous mammary carcinomas that appear in the records of the Crocker Institute, excluding those that had multiple tumors on arrival and those in which a new tumor might have been confused with an autoplast, and counting only those in which new tumors arose at a site far removed from the first one, there were 10 in which second tumors were discovered after the mice entered the laboratory. Of these, three developed a third tumor. The time after reception at which second neoplasms were found ran from 10 to 135 days, and when a third appeared the interval elapsing between its discovery and that of the second was four, fourteen, and twenty-eight days. Not a few of the later tumors grew rapidly.

As nothing is known of the proportion of these mice in which only one tumor arises, no conclusion can be drawn from such figures, except that mice with one spontaneous mammary carcinoma develop a second one with fair frequency, and sometimes even a third; and they have been cited only to show the intricacy of the problem under discussion. For while it must be true that the factor which excites the development of spontaneous carcinoma is not so violent an agent as tar, it nevertheless was able to produce a second tumor when tar would have failed in the breed of mice with which Murray worked.

Yet if the current view is correct, that a violent stimulus may override constitutional resistance to carcinogenesis, exactly the opposite situation would be expected—entire absence of subsequent spontaneous tumors in mice with a spontaneous carcinoma, but the easy production of tar tumors in such animals.

The only one who has been able so far to corroborate Murray is Cramer,[60] a fact which seems to me highly significant since it may be safely assumed that he employed the tar and the strain of mice which were used in Murray's experiments. It may very well be, therefore, that variations in the results obtained by the British investigators and those in other countries depend on differences in the mice, the tar, or the method of application.

Site and Susceptibility.—Another aspect of the question of soil is the relative susceptibility of different areas in the same animal. Burckhardt and Müller [44] noted that tumors appeared much later at the root of the tail than on the back, but there were only four mice in their experiment. Burckhardt [43] later recorded an experiment in which multiple painting had been carried out to determine whether one part of the body was more responsive than another. The skin of the back in mice was found most reactive and that of the snout and the groin much less so; but whether this was because the tar could be more easily removed from some sites than from others the author did not wish to discuss at that time.

Roussy, Leroux, and Peyre [235] found that when tar was applied along the whole length of the vertebral column, tumors generally developed only in the interscapular region. If multiple growths did arise along the tarred tract, they appeared first at its cervical end; and tumors in that location grew faster and looked more malignant under the microscope than those originating at the caudal end of the tarred streak. They concluded, therefore, that the skin of the same mouse is not uniformly susceptible.

Bonne [37] pointed out that papillomas are often found on the neck in tarred rabbits, where the skin is in contact with a painted ear. To determine whether the skin of the back is as reactive as it is in the mouse, two rabbits were painted in the sacral region, a procedure which resulted in the appearance of carcinoma within two and a half months.

All investigators have noticed that tar tumors do not develop throughout the tarred area but only at isolated points, a feature which they share, according to Halberstaedter,[100] with roentgen-ray carcinoma and that found in sailors and farmers as a result of exposure to the sun's rays. Several writers have therefore suggested that only a cell or two here and there may be responsive to the irritant, and that those in healing wounds may be especially labile.

Coat Color.—In discussing individual predisposition, Yamagiwa and Itchikawa [275, 277] expressed the opinion that black or black and white rabbits were perhaps somewhat more susceptible than those of lighter color, but they were unwilling to say definitely that this was so until parallel experiments on pure blacks and pure whites had been carried out.

This has now been done by Leroux and Simard,[158] who painted six white and six black rabbits two or three times a week for six months, discontinuing the applications at the end of this period. Tumors appeared earlier and more frequently, and reached a larger size, in the black rabbits. So far as I am aware, no such comparison has been made in the mouse.

That albino rabbits are not exempt, however, is shown by their experiment, as well as by the observations of Ciechanowski, Morozowa, and Wilhelmi,[57] who tarred 12 such animals. In the majority of them tumors were produced which exhibited the microscopic features of the papillomas and precancerous lesions described by other investigators.

Age and Sex.—Nobody has noticed a distinct predisposition in either sex, nor has age proved to be a definite factor in etiology. However, Yamagiwa and Itchikawa [274, 277] suggested that females might be a little more susceptible than males, but explained that they had used more females in their work. They found, also, that only rabbits over seven or eight months of age reacted to tar.

Ciechanowski and Morozowa [56] regarded age as a factor of no importance in the initiation of tar cancer in the rabbit.

In the mouse, Fibiger [83] said that neither age nor sex was of significance, and Roussy, Leroux, and Peyre [233] were of the same opinion.

Bang (cited by Yamagiwa [271]) produced cancer after three or four months of tarring in mice that were but from nineteen to thirty-four days old when the experiment was begun, while Leitch [153] could find no difference in the yield of tumors from adult mice and those under six weeks of age.

Polettini [218] also has investigated this question and has found age to be of no moment.

Parodi [204] reported the production of tumors in mice that were only about two months old when tarring was begun. When his paper was written, they were seven or eight months of age; some had only small papillomas, while others, especially the females, had large ulcerating neoplasms. As there were only sixteen mice in his series, this greater susceptibility among females may well have been illusory.

Thus it appears to be the case, as Leitch has said, that the important factor in carcinogenesis is not the age of the animal in itself, but the length of time during which the irritant has acted.

Light.—Another factor relating to the general condition of the animal is light, which appears neither to favor nor to delay carcinogenesis, since Bang [4] discovered that mice kept in complete darkness developed tar cancer as quickly as their controls. It will be remembered, too, that Lipschütz could trace no connection between the presence of light and the occurrence of melanomas.

Heredity.—Heredity is regarded by Parodi [206] as of no special importance. However, he had but a small number of mice in his series, and experiments of this sort should be carried out on a really large scale. It is to be hoped, therefore, that this work will be repeated with an adequate number of animals.

An excellent beginning has been made by Miss Lynch,[170] who showed that two strains of mice, one with a high and the other with a comparatively low incidence of spontaneous mammary tumors, developed tar cancer of the skin with practically identical frequency. She suggested, however, that a high incidence for the mammary gland did not necessarily mean a high incidence for another tissue, such as the skin.

Surface Tension.—Finally, Bauer [11] has proposed that the factor common to those lesions produced by chronic inflammation, aniline dyes, tar, the roentgen ray, parasites, and repeated mechanical irritation may be a lowering of the surface tension of the body fluids.

Local Factors.—The main discussion on the influence of local conditions on the development of tar cancer has centered about the relations between epithelium and connective tissue.

Relation Between Epithelium and Connective Tissue.—Borst [41] has suggested as the most probable cause a disturbance in the equilibrium between the two, in the course of which the epithelium undergoes some sort of deviation from the normal, and the great majority of investigators seem disposed, like Borst, to place the initiative with the epithelium, although many regard the connective tissue as a factor of considerable importance.

Yamagiwa and Itchikawa [277] wrote of the emancipation of the epithelium, and of a mucoid degeneration of the connective tissue which they ultimately came to regard as of minor importance, whereas Itchikawa and Baum [114] were inclined to think that the emancipation and dissociation of the epithelium were secondary to alterations in the connective tissue.

Murray [197] doubts the value of the conception that a resistance to unrestricted growth is gradually removed, believing it more probable that the cancer cell acquires new properties—exploitations of normal cell activities which act in a new way and with disastrous consequences to the organism.

Sczcelik,[247] as well as Dreifuss and Bloch,[80] was also inclined to discount the importance of the changes in the connective tissue, and much the same view is held by Bang,[3, 7, 8] who has discussed the cancerization of the epithelium; by Deelman,[69] who has described the fundamental changes which this layer undergoes; and by Champy and Vasiliu,[55] who, like Leitch,[154] have suggested that regeneration is gradually converted into malignant proliferation. But while Bang,

Champy and Vasiliu, and Leitch all thought of epithelial change as the fundamental factor in carcinogenesis, there is some difference in their views of the exact nature of this alteration, for Bang has expressed the belief that cell multiplication and cancerization are two entirely different processes.

Bierich [19] and Bierich and Rosenbohm [25] have offered a hypothesis based on Warburg's investigations on the carbohydrate metabolism of the cancer cell. According to their belief, the increased breaking down of reserve carbohydrate by the cancer cell causes the appearance of lactic acid, which permeates the connective tissue and by transforming its collagen fibrils into a gelatinous material favors penetration by the epithelium.

After an extensive review of the various methods that have been employed to excite malignant growth, and a consideration of xeroderma pigmentosum, roentgen-ray cancer, and malignant tumors in general, Bommer [34] arrived at the conclusion that such changes in the connective tissue as atrophy and edema may be of considerable importance in the establishment of malignancy.

Even if it were possible to assign the chief rôle to the epithelium, as most pathologists are inclined to do, there is not the slightest conception at present of the manner in which malignant transformation is accomplished, although it has been proposed by Schuster [24a] and by Teutschlaender and Schuster [25b] that mitotic anomalies, at any rate, are probably not concerned. Division figures in the skin of tar-painted mice were found to preserve their normal appearance until carcinoma had set in, and even then they were abnormal only in undifferentiated cells. Unless some alteration that escapes the microscope is involved, we must therefore seek in some other direction for the initial changes of neoplasia.

Bittmann [26] thought it possible that tar might attack first the centrosome, as Kappers had suggested, for this is the dominant factor in normal cell division and the only structure which passes unchanged through all three stages. In any case, he had found, before nuclear division in the tarred epithelium of the rabbit, more than two centrosomes of unequal size and staining properties.

Teutschlaender and Schuster,[25b] however, were unable to see the centrosomes clearly in their preparations, but pointed out that any damage to these structures would probably be reflected in irregularities of mitosis, such as they had been unable to demonstrate in tar cancer.

Daels,[61] who injected tar under the skin of mice and then painted the site with tar, saw no tumor arise among six animals so treated, even after 100 days. He accordingly suggested that cells which are to be subjected to repeated irritation in the expectation of inciting cancer must be in a relatively normal condition.

Nerve Supply.—The influence of nerve supply on the initiation or the subsequent growth of tar cancer has been discussed in four recent papers. Auler [1] resected the cervical sympathetic ganglion of one side in an unmentioned number of rabbits, and painted these animals and a group of normal controls with tar. When his paper appeared no changes had been produced in the animals on which operation had been performed, although the controls had developed papillomas and carcinomas.

According to Itchikawa and Kotzareff,[118, 140a] resection of the anterior or posterior auricular nerve in rabbits seemed to cause the regression or disappearance of established tumors in the corresponding area, even when tarring was continued after the operation. An experiment in which resection of the same nerves preceded tar painting did not give conclusive results, but resection of a cervical sympathetic ganglion appeared to favor the development of tumors when the corresponding ear was painted. However, the authors wished these experiments to be regarded as merely preliminary.

On account of the contradictory reports of Auler and of Itchikawa and Kotzareff, Rémond, Bernardbeig and Sendrail [222] repeated the experiment, and found that their results confirmed most often those of Itchikawa and Kotzareff. In rabbits that had been subjected to neurectomy, the development of tar tumors seemed to be delayed on the side on which operation had been performed. Two animals had no tumors at all in the ear deprived of communication with the cerebrospinal system, although the opposite ear was the seat of a large number, while in the remaining one of this group the two ears were equally affected. Section of the cervical sympathetic trunk hastened the formation of tar tumors or accelerated their growth in four of six rabbits. In the one rabbit in which neurectomy and sympathectomy were combined, the stimulus provided by section of the sympathetic prevailed. The authors proposed that the sympathetic might exert its control by means of the blood vessels.

The relation between innervation and carcinogenesis has been investigated also by Cramer,[59] who has summarized the three possibilities somewhat as follows: 1. The presence of innervation is not an essential factor; then the application of tar to a denervated area of skin should produce cancer as readily there as on the normal skin. 2. The absence of innervation predisposes to cancer; if that were so the production of cancer by tar painting should be accelerated in a denervated area. From the premise that malignant new growths are devoid of nerves, it has been concluded that the absence of nerve control is, if not the cause, a material factor in the origin of cancer. But even though this premise be correct, the conclusion does not necessarily follow. 3. Innervation is an essential factor in the process of chronic irritation

which leads to cancer. In that case, denervation would delay or inhibit the production of cancer by tar.

A piece of skin on the back was completely severed from the surrounding skin and from the underlying tissues, and then sewn into position again so as to form an autoplast temporarily freed from nervous control. In twenty mice the autoplast healed successfully into place. In the second series, of twenty-three mice, an elongated flap was cut which remained connected anteriorly with the skin of the back in the middle line by a bridge of tissue from 3 to 4 mm. in breadth. After this flap had been completely separated from the underlying tissues, it was stitched back into place. At the end of nine months, twelve of the seventeen surviving mice had developed tumors on the normal skin, but only five of the twelve had one also on the autoplast or flap. Among these five, the tumor on the autoplast developed before the tumor on the normal skin in only one, while in three the tumors appeared very late on the autoplast, requiring more than seventy paintings twice weekly.

Cramer explained that in interpreting these results it must be taken into consideration that nerve regeneration presumably took place, so that the autoplast remained completely free from nervous control only during the first two or three months after operation. Thus the difference between the normal skin and the autoplasts or flaps gradually disappeared, and with it the difference in the reaction to chronic irritation. This would account for the three tumors that appeared after more than eight months of painting.

Cramer concluded that lack or impairment of nervous control in an area of skin does not cause cancer, or even predispose to it. On the contrary, there was clear indication that in the process of chronic irritation which leads eventually to the development of cancer the presence of efficient nervous control is an important factor.

Cell Crowding.—A unique hypothesis to cover the action of tar has been offered by Burrows and Johnston.[45] The previous work of Burrows had convinced him that cell crowding is followed by the accumulation of "archusia," a term coined to designate the driving factor of the cell, and by separation of the colony from intercellular substance and blood vessels. When a suitable concentration of archusia has been attained, the outcome is independent growth or malignant disease.

The action of tar was explained in the following way. Cells migrate, or draw fats and proteins to themselves, through their "ergusia," the laboring substance of the cell. If a more or less immobile and indigestible substance with strong affinities for ergusia is placed in the tissues, cells will be drawn to it and away from their intercellular substance and blood vessels, collecting in a dense and stagnant mass: in other words, the conditions will be given for the inception of a malignant tumor.

I have not yet been able to grasp all the intricacies of this hypothesis, of which the two preceding paragraphs are acknowledged to be an imperfect account, but at present I can see little difference between archusia and energy, or between ergusia and chemotaxis. Nor can I understand the genesis of sarcoma, since connective tissue elements and their intercellular substance are almost inseparable. But as sarcomas do arise, and as tar should act, by hypothesis, as well on connective tissue as on epithelium, both sarcoma and carcinoma might be expected to follow inevitably the application of tar. Finally, although all must admire the amount of labor and thought which Burrows has expended in shaping his hypothesis, it must be admitted that it does not, in its present form, elucidate the fundamental problem of cancer: Why does not every tarred mouse develop a malignant tumor, and why is tar inoperative for the skin of the guinea-pig and the rat?

Burrow's ideas have been elaborated by his associate, Jorstad,[124, 125] who has recently affirmed that vitamin A protects against the destructive action of coal-tar, whereas vitamin B stimulates the growth of cells gathered about injected particles of tar.

Some support has been lent, too, by the observation of Fischer,[90] who found that cell division did not occur in isolated fibroblasts, but only in those that were crowded together.

Nevertheless, the work of Greenleaf [98] does not suggest that this is a phenomenon of general applicability, for no evidence could be discovered to suggest that infusoria elaborate a substance that hastens their division rate. On the contrary, the excretion products of these organisms was inimical to reproduction, and Greenleaf saw in his experiments no support for the contention of Robertson that cells mutually accelerate their division rate by setting free a chemical agent or "autocatalyst."

Allergy.—Kimla [136] has offered the suggestion that cancer may represent a reaction to repeated stimulus which is analogous with the reaction to tuberculosis in an organism that has been rendered allergic. The basis for this proposal was an experiment in which benign tar papillomas had been produced on a rabbit's ear; thirteen months after tarring of the ears had been discontinued, painting was resumed near the root of the tail, and two months later a sudden hyperemia of the ear set in accompanied by the development of carcinoma.

Comparison of Tar with the Rous Principle.—Carrel [51, 52, 53] found no fundamental difference in tissue cultures between the Rous sarcoma and a tar sarcoma of the fowl, for in both it was the macrophage rather than the fibroblast which carried the malignant characteristic. He ascribed malignancy to a metabolic disorder of the cell, determined by an agent elaborated in the tissues under the influence of such nonspecific factors as tar, arsenic, certain parasitic worms, the roentgen ray, etc.

With Landsteiner, Carrel [50] attempted to transform a pure strain of fibroblasts into sarcoma by adding small amounts of coal-tar to the cultures, but although exposure was continued for months, malignant growth could not be excited. Similar experiments with the macrophage were equally unsuccessful. Hence it was concluded that the mode of action of tar must be quite different from that of the active principle of the Rous sarcoma, which can change the macrophage into a sarcoma cell, in vitro, in as short an interval of time as forty-eight hours.

It was then postulated that tar might be the precursor of some substance, analogous to the Rous principle, which developed in the tissues under the influence of two factors—local irritation, and some modification induced by the tar in the blood plasma. This hypothesis inspired an experiment in which intravenous injections were made into fowls with a solution of coal-tar, and subcutaneous injections with embryo pulp. As a result of this procedure the fowls developed teratomas which were partly sarcomatous, and which not only recurred after extirpation, but also proved to be transplantable into other chickens.

Parasitic Hypothesis.—The parasitic hypothesis has been reexamined in the light of what has been learned from tar cancer, but has once more been found wanting. Thus Leitch [155] has pointed out that his production of carcinoma of the gallbladder with sterilized pebbles demonstrated that no living virus was operating.

It has been said by Romme and Harde [226] that partisans of the virus hypothesis of cancer ascribe failures to communicate the disease by filtered emulsions to a lack of adaptation between virus and normal tissue. But the inoculation of filtrate from a transplantable mouse tumor into mice that had been tarred long enough for their lesions to have reached the precancerous stage was entirely unsuccessful in ten mice.

Lubarsch [168] thought that the parasitic hypothesis, in the sense that there is a specific cancer parasite, had been entirely destroyed, for he found it impossible to believe that during the application of tar, in whatever country this was done, the identical parasite could be fortuitously introduced.

SUMMARY

The importance of extrinsic factors in the causation of certain varieties of neoplasm becomes more and more apparent. But while those known at present are such as will excite chronic inflammation, the etiologic agent must be peculiarly adapted to the tissue if it is to be operative, since not all irritating materials are carcinogenic. Apparently, too, there are grades of specificity. Fibiger's parasite, for example, affects only the epithelium and Bullock's only the connective tissue, but tar will incite either one to malignant growth.

Susceptible species need not be closely related; thus tar will evoke cancer in the skin of the mouse but not in that of the rat, yet it is carcinogenic for man.

Perhaps the most interesting discovery that has come from the study of experimentally produced tumors is the unimportance of age, for it had been universally assumed that this plays a fundamental rôle in neoplasia. It now appears to be true, however, that not the age of the body but the duration of the irritation is the decisive factor, and that when those preliminary changes which are to culminate in malignancy have been initiated, a tumor will follow even though the irritant is withdrawn.

The relative importance of irritant and soil, the part played by heredity, the significance of general poisoning in the inception of tar cancer, the cell changes preceding malignant transformation, and other fundamental problems which can now be attacked with some chance of success, are not yet ripe for discussion, though some progress has been made with all. Technical difficulties still threaten to postpone their solution for a long time, still it must not be forgotten that less than fifteen years ago the possibility of inducing malignant growth at will seemed equally remote.

The realization of that possibility, one of the most significant victories of modern medicine, encourages the hope that even the problem of controlling cancer will be ultimately solved.

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Notes and News

Honors in Memory of Harold C. Ernst.—A special room to be used as a library has been presented to Harvard Medical School in memory of Harold C. Ernst, 1856-1922, its first professor of bacteriology. In this room has been hung an oil painting of Dr. Ernst, and a bas-relief of him has been unveiled in the hall of the main building of the school. Harold C. Ernst was the secretary of the Association of American Pathologists and Bacteriologists from its foundation in 1901 until 1917, and he was also the editor of the first forty-three volumes of the *Journal of Medical Research*, which began as the *Journal of the Boston Society of Medical Sciences* and which became the *American Journal of Pathology* in 1925.

State Cancer Hospital and Clinics in Massachusetts.—Dr. George H. Bigelow, Massachusetts State Commissioner of public health, has announced the appointment of an advisory committee to assist his department in carrying out the provisions of the cancer bill, passed by the legislature in the closing days of the session. Under the bill the Norfolk State Hospital is to be converted for use as a hospital for treatment in advanced stages of cancer, and $100,000 is appropriated for this purpose. The bill provides an additional $15,000 for the establishment of cancer clinics.

Awards of Prizes.—The Hungarian Academy of Science has awarded the academy prize for this year to E. Krompecher, professor of pathology in the University of Budapest, for his work on cancer.—Dr. Karl Landsteiner, a member of the Rockefeller Institute for Medical Research, has been awarded the annual prize of the Dr. Hans Aronson-Stiftung, Berlin, in recognition of his work on antigens and antibody formation.

Memorial to Beaumont.—A memorial has been unveiled at Lebanon, Conn., to Dr. William Beaumont, the pioneer American physiologist and member of the U. S. Army Medical Corps. Beaumont was born in Lebanon, Nov. 21, 1785, and the memorial is a tablet set on a boulder from the Beaumont farm. It will be recalled that he made most of his observations on Alexis St. Martin, a Canadian, who suffered a permanent gastric fistula, following an accidental gunshot wound. The Michigan Medical Society, to which Beaumont reported his studies in 1827, erected a monument to him on Mackinac Island near the spot where this epochal work was begun.

Recommendations of Pathological Society of Great Britain and Ireland For Prevention of Sepsis in the Postmortem Room.—I. Strong postmortem gloves, not too thick, should be worn, and should be thoroughly cleansed, sterilized and dried immediately after use. Great care should be taken to ensure that there are *no holes*. A convenient way is to fill them with water, twist the wrist portion round until it is closed off and then, by pressure, test for pin-holes. The same result may be achieved by air pressure after the gloves have been dried: in this case the glove should be turned about close to the face while pressure is exerted on the contained air.

II. It is inadvisable to perform necropsies when there are *recent* cuts or scratches on the hands. In case of necessity, a protective covering of collodion may be used.

III. The greatest danger of all, and the one chiefly responsible for serious and fatal infections, is *pricking the finger.* If during a necropsy the pathologist should prick himself however slightly, whether with the knife or on a jagged bone or tooth, even if he is in doubt whether he has been pricked at all, it is his duty *to stop* AT ONCE, *remove his glove, and make the wound bleed* by digital compression causing congestion, by centrifugal force (swinging the arm), by sucking and by putting the hand in hot water. There should not be a minute's delay in carrying out these procedures, and the necropsy should be completed by some one else.

British Collection of Type Cultures.—A new catalog of the British national collection of type cultures has been issued, which lists over 2,000 living strains of bacteria. The collection was under arrangement with the Lister Institute, where the collection is housed. Its object is the collection and maintenance of authentic strains of recognized bacteria and protozoa for use in scientific work. It includes both pathogenic organisms and strains of economic significance, while it has recently added cultures of fungi of importance in plant pathology, medicine, veterinary science, technology and soil bacteriology. The staff is willing to help in the identification of strains received from workers both at home and abroad; and last year more than 4,000 cultures were distributed to workers throughout the world.

Death of John George Adami.—Dr. John George Adami, from 1892 to 1919 professor of pathology and bacteriology in McGill University, Montreal, and since then vice chancellor of the University of Liverpool, died Aug. 29, 1926, aged 64. Dr. Adami was born in Manchester, England, and educated there at Owens College. He took his medical work at Cambridge, and after serving as house physician in the Manchester Royal Infirmary, became demonstrator of pathology in the University of Cambridge in 1887. He was pathologist in the Canadian department of agriculture from 1897 to 1902. While at McGill University Dr. Adami, who was an able and successful teacher, took an active and influential part in the development of scientific medicine in Canada and in the United States. He was president of the Association of American Physicians in 1911. He was a fellow of the Royal Society and numerous other scientific bodies, and the recipient of high academic honors. He was the principal author of "Text-Book of Pathology" and "Principles of Pathology," and wrote many papers of pathologic and bacteriologic interest. His article on inflammation in Allbutt's "System of Medicine" attracted much favorable notice. During the war he was assistant director of medical services in the Canadian Army Medical Corps, and he subsequently was the historical recorder of the medical services of the Canadian expeditionary forces. As vice chancellor he proved to be an able administrator and an energetic apostle in the interests of university education.

Obituary

ALLEN JOHN SMITH, M.D.

1863—1926

On Aug. 18, 1926, Dr. Allen John Smith, professor of pathology and of comparative pathology and director of the courses in tropical medicine, University of Pennsylvania, died at his home at St. Davids, Pa.

He was born at York, Pa., on Dec. 8, 1863, the son of the late Gibson and Susan Elizabeth Fahs Smith. For several generations his ancestors on both sides have lived in Pennsylvania as prosperous merchants and farmers.

Dr. Smith was prepared for college at the York Academy. He received his A.B. from Gettysburg in 1883, and his M.D. from the University of Pennsylvania in 1886. In 1910 his first alma mater honored him with the Sc.D. degree. Both McGill University (1911) and Gettysburg (1921) bestowed on him the degree of LL.D.

After completing his internship at the Philadelphia General Hospital ("Blockley"), Dr. Smith became assistant demonstrator of pathology at the University of Pennsylvania under the late Dr. Guiteras. In 1891, he was called to the medical department of the University of Texas as professor of pathology, where he remained until 1903 serving for part of the time as dean of the medical school. Then he returned to the University of Pennsylvania as professor of pathology (1903-1926). Since 1911 he also had been head of the department of comparative pathology and the courses in tropical medicine. In addition to his teaching duties, he acted as dean of the medical faculty from 1909 to 1912.

During the World War he was on active duty as commanding officer of the laboratory at Camp Dix, N. J., and at Camp Pike, Ark., from June 20, 1918, to March 22, 1919, with the rank of Major, M.C. Since May 19, 1919, he had ranked as lieutenant colonel in the Medical Reserve Corps.

Dr. Smith was a member of many learned societies and made important contributions to medical science. He discovered *Bacillus coeruleus* (*Pseudomonas smithii*) at the beginning of his professional career (1887). His work on hookworm disease was fundamental and established conclusively that this disease was epidemic in this country; subsequently Stiles demonstrated that the particular species of hookworm involved in this country was a new one.

He also produced evidence implicating bedbugs as carriers of leprosy infection, and ticks as harboring larvae of certain filarial worms.

He elucidated the periodicity of microfilariae in the peripheral blood of hosts. Medical parasitology owes to him the description of many new species.

In 1914, Dr. Smith (in collaboration with Dr. M. T. Barrett) brought forward again the virtually forgotten mouth ameba, and attributed to it an important part in producing pyorrhea alveolaris, with the further proposal to treat the condition by emetine as an amebicide.

ALLEN JOHN SMITH, 1863-1926

His position has frequently been assailed, mostly under the mistaken belief that the ameba had been heralded as the sole cause of the condition; many others, however, have accepted the proposition that the ameba, in more or less symbiotic relation with a variety of bacteria, is a causative agent. Whatever may be the ultimate decision, his work has unquestionably stimulated a more careful study of mouth infection by both the medical and the dental professions.

His breadth of interest may be illustrated by citing the titles of his books: Classbook in Bacteriology; translations of Kitt's Comparative General Pathology, and of Fürth's Problems of Physiological and

Pathological Chemistry of Metabolism; and sections in several textbooks on legal medicine. His interests, in fact, embraced the entire field of pathology.

What of the man himself? He is still so near to us that it is difficult to pay full tribute to a man who was beloved by every one with whom he came in contact, to whom student, stranger, staff and colleagues turned for help and wise counsel, who gave generously of himself and of his time, whose sense of duty to his work and to his students was an example for every one, though few could live up to his high standards. He was far more than the chief to his staff, for he took a personal interest in both the professional and the personal welfare of the members.

Thus ended a life full of activity and achievement, of kindliness and generosity, and of high ideals. His alma mater loses one of her best beloved teachers, and pathology a master.

BALDWIN LUCKÉ.
MORTON MCCUTCHEON.

Abstracts from Current Literature

Pathologic Physiology

THE INFLUENCE OF THE TESTES ON METABOLISM. E. P. BUGBEE and A. SIMOND, Am. J. Physiol. **75**:542, 1926.

Working with castrated dogs, the authors failed to find any evidence that castration in itself effects a reduction of basal metabolic rate. The factors actually operating in this condition to reduce metabolism they believe to be lack of psychic stimulation, lack of muscular exercise and adaptation of the nervous and endocrine systems to a life less active than normal.

H. E. EGGERS.

THE EFFECT OF PANCREATECTOMY ON THE SECRETION OF SUCCUS ENTERICUS. W. KOSKOWSKI and A. C. IVY, Am. J. Physiol. **75**:640, 1926.

In pancreatectomized dogs the quantity of succus entericus is not materially affected. Invertase content is definitely increased for several days, then tends to return to a value slightly greater than normal. Amylase content is temporarily increased, lipase content is unaffected. For the eighteen days following pancreatectomy there are no compensatory changes in the succus entericus which would facilitate intestinal digestion.

H. E. EGGERS.

A METHOD FOR SEPARATING THE AIR BREATHED BY THE RIGHT AND LEFT LUNGS, TOGETHER WITH THE EFFECT OF PULMONARY CIRCULATORY CHANGES ON THIS DIVIDED BREATHING. EDWARD D. CHURCHILL and ANNA AGASSIZ, Am. J. Physiol. **76**:6, 1926.

A method of collecting air from either lung separately, along with optional interference with the pulmonary circulation, is described. The effects of the latter procedure on volume of respiration were studied in the cat. It was found that occlusion of one branch of the pulmonary artery was without effect on volume of movement. Occlusion of the left pulmonary vein, on the other hand, was accompanied by a marked increase of respiration on the left side. The necessary increase of volume resulting from the combination of capillary distention and increased alveolar air space the authors believe may be achieved by encroachment on adjacent areas of lung, and they suggest that a similar mechanism may be a factor in the production of compensatory emphysema.

H. E. EGGERS.

THE EFFECT OF FEEDING THYROID EXTRACT ON GASTRIC SECRETION. CHARLOTTE TRUESDALE, Am. J. Physiol. **76**:20, 1926.

Following the feeding of thyroid extract to Pavlov pouch dogs, the usual results of loss of weight, increased pulse rate and body temperature, and increased restlessness, were observed. These were accompanied by a slight diarrhea. In all cases there was a diminished gastric secretion, both in the continuous secretion and that following a meal.

H. E. EGGERS.

STUDIES ON GASTRIC FUNCTION IN PULMONARY TUBERCULOSIS, INCLUDING AN ANALYSIS OF GASTRIC FUNCTION IN 198 CASES OF PULMONARY TUBERCULOSIS. D. PERLA, Am. Rev. Tuberc. **13**:317, 1926.

Pulmonary tuberculosis is generally accompanied by hypo-acidity, which does not necessarily parallel the extent of the involvement, but which is usually of a higher degree in patients with constitutional symptoms. All patients with emetic cough showed marked hypo-acidity. Anacidity was found in some patients without any gastro-intestinal complaints. Gastroptosis does not seem to impair the chemical functions.

MAX PINNER.

EXPERIMENTAL RENAL INSUFFICIENCY. THE EFFECTS OF HIGH PROTEIN DIET IN THE PRESENCE OF LOW RENAL FUNCTION ON THE KIDNEYS, AORTA AND LIVER; CHANGES IN THE BLOOD PRESSURE AND CONCENTRATION OF BLOOD METABOLITES. I. CONTROLS ON NORMAL DIET. H. ANDERSON, Arch. Int. Med. **37**:297, 1926.

A condition of low renal function simulating the reduced kidney filter of chronic renal disease was produced in rabbits by removing portions of the kidneys by surgical means. Between 60 and 70 per cent of the total kidney substance was destroyed in this way. Following the operative procedures in which over 60 per cent of kidney substance was destroyed, there was a retention of creatinin and urea nitrogen in the blood. There was no increase in blood pressure following the reduction of kidney substance, even in those which died from a slowly progressive renal insufficiency. All in the second group died of renal insufficiency. The kidney remnant uniformly showed hypertrophy. Only four showed no gross or microscopic signs of obstruction. These four all showed diffuse hydropic change, which was probably due to overactivity The aorta appeared normal at necropsy. The liver in some exhibited fatty metamorphosis.

S. A. LEVINSON.

EXPERIMENTAL RENAL INSUFFICIENCY. THE EFFECTS OF HIGH PROTEIN DIET IN THE PRESENCE OF LOW RENAL FUNCTION ON THE KIDNEYS, AORTA AND LIVER; CHANGES IN THE BLOOD PRESSURE AND CONCENTRATION OF BLOOD METABOLITES. II. PROTEIN DIET EXPERIMENTS. H. ANDERSON, Arch. Int. Med. **37**:313, 1926.

Removal of two thirds of the kidney substance in rabbits results in a retention in the blood of urea and creatinin, which either increases progressively in intensity until death results, or decreases progressively until normal values are once more attained. If the renal insufficiency is not progressive, the kidney remnant undergoes hypertrophy. A high protein diet causes hypertrophy of the kidneys in normal rabbits not operated on. A high protein diet causes no further change in the kidney remnant than to further augment the hypertrophy. A high protein diet causes a retention of creatinin and urea in the blood in rabbits from which a portion of kidney substance has been removed. It is proportionate to the amount of kidney which has been removed. The retention does not occur in normal rabbits. Hypertension is not caused in rabbits by renal insufficiency per se; nor by a high protein diet even in the presence of a low renal function; nor by prolonged retention of creatinin and urea in the blood. The high protein diet here given results in a marked atherosclerosis of the aorta which does not extend to the small arteries. These changes in the aorta do not result from low renal function or from prolonged retention of creatinin and urea in the blood.

S. A. LEVINSON.

SOME METABOLIC ASPECTS OF CALCIUM THERAPY. A. P. BRIGGS, Arch. Int. Med. **37**:440, 1926.

Calcium acetate given by mouth causes the diversion of a considerable amount of the excreted phosphoric acid from the urine to the feces. The relief from this phosphoric acid load necessitates the synthesis of a smaller amount of ammonia by the kidney. The administration of calcium acetate affords a means of correcting the phosphoric acid retention in nephritis free from the disadvantages of alkali retention and resulting edema which is observed with sodium bicarbonate therapy.

S. A. LEVINSON.

EFFECT OF JEJUNOSTOMY IN EXPERIMENTAL OBSTRUCTION OF THE JEJUNUM OF THE DOG. RUSSELL L. HADEN and THOMAS G. ORR, J. Exper. Med. **43**:483, 1926.

Jejunostomy does not prevent the development of the chemical changes of the blood characteristic of obstruction of the jejunum in the dog.

Jejunostomy following experimental obstruction of the jejunum has no beneficial effect on the duration of life. There is some evidence that life may be shortened by early jejunostomy.

Treatment of jejunal obstruction with sodium chloride solution tends to prolong the life of animals regardless of jejunostomy.

AUTHORS' SUMMARY.

THE RELATION BETWEEN ATHEROSCLEOSIS AND INGESTED CHOLESTEROL IN THE RABBIT. SARAH CLARKSON and L. H. NEWBURGH, J. Exper. Med. **43**: 595, 1926.

By feeding large doses of cholesterol to rabbits, it is possible to produce hyperchlosterolemia and atherosclerosis in a few weeks. When rabbits are fed on a high protein diet the same changes may develop, due, it is believed, to metabolic disturbances caused by the excess protein.

AUTHORS' SUMMARY.

EXOPHTHALMIC GOITER IN THE PACIFIC NORTHWEST. J. MASON, Surg. Gynec. & Obst. **42**:663, 1926.

Goiter is one of the great problems in the state of Washington. It has been estimated that 65 per cent of the boys and 75 per cent of the girls between 12 and 18 years have some enlargement of the thyroid. There are districts east of the Cascade Mountains in which all domestic animals have some disturbance of the thyroid. The Indians and dogs in this district were the only living things that had no thyroid involvement, due, it is believed, to consumption of stripped salmon. The water in the northwest country is low in iodine, and the municipalities are beginning to realize this fact. When this deficiency will be properly supplied, goiter, Mason thinks, will be eradicated.

M. L. PARKER.

Pathologic Anatomy

A RARE CASE OF MULTIPLE CONGENITAL ATRESIA OF THE ILEUM WITH COMPLETE SEPARATION OF A SEGMENT OF BOWEL. I. H. ERB, Am. J. Path. **2**:137, 1926.

An interesting case of multiple atresia of the ileum with complete separation of a segment of bowel is here reported. Such an isolated segment is, so far as we have been able to determine, peculiar to this case. The absence of bile pigment below the upper atresia would indicate that the occlusions had occurred

before the third or fourth month of intra-uterine life. The presence of a peritoneal adhesion suggests that the cause of these atresias was an early intra-uterine peritonitis.

AUTHOR'S SUMMARY.

ADENOMA OF THE SALIVARY GLAND. CARL B. SCHUTZ, Am. J. Path. **2**:153, 1926.

An adenoma of the parotid gland encountered in an 18-year old girl is reported. The duration was three years, with slow growth and slight pain. It was encapsulated, and microscopic examination showed the epithelial elements varying in their arrangement from undifferentiated columns of cells to formed acini.

AUTHOR'S SUMMARY.

CYSTITIS EMPHYSEMATOSA. WILHELM HUEPER, Am. J. Path. **2**:159, 1926.

The report of a case with cystitis emphysematosa in a female dog is given. Bacteria could not be detected in the tissue, therefore a direct infectious origin could not be substantiated. The production of gas may be due to absorption of bacterial enzymes from the urine containing glucose. The restriction of the cystitis emphysematosa to the female sex is possibly only accidental owing to the small number of the cases observed and the greater frequency of the predisposing factors in the female sex.

AUTHOR'S SUMMARY.

STUDIES ON THE EFFECT OF CHLOROFORM ON THE LIVER OF RABBITS. EDMUND DE ZALKA, Am. J. Path. **2**: 167, 1926.

The necrobiotic processes in the liver from subcutaneous injections of 0.5 to 1.25 cc. of chloroform have been studied. Three and six hours after the injection, there are no pathologic changes. Twenty-four hours after the injection and later until four and one-half days, well marked necrosis of the central parts of the lobules is visible. The necrosis is hyaline in character, with cells having pyknotic nuclei. The absence of polymorphonuclear leukocytes is striking. In the livers with extensive necrosis, no glycogen is present. A relatively small amount of fat is found in the necrotic cells, but there is a considerable amount of fatty liver cells at the border between the necrotic and normal areas. We find lime salts in the necrotic cells in 80 per cent of the necrotic livers, so we consider this characteristic at least in rabbits. In the necrotic areas, the endothelial cells are increased in number and form giant cells. The elimination of the necrotic cells is accomplished mostly by the phagocytic action of cells of endothelial origin. Four and one-half days after the poisoning most necrotic cells have disappeared. The regeneration takes place very soon, as a rule on the third day; mitotic figures are regularly seen in the normal liver cells.

In three rabbits the chloroform was administered for longer periods. In these cases no extensive necrosis was present. In the liver of these rabbits, there were giant cells and large vacuolated cells in which neither fat nor glycogen was demonstrable. In one of these cases a distinct increase of connective tissue was seen around the central veins and less pronounced in the periportal spaces.

AUTHOR'S SUMMARY.

TISSUE REACTIONS TO RADIATION. JAMES EWING, Am. J. Roentgenol. **15**:93, 1926.

Ewing summarizes the knowledge of roentgen-ray therapy in tumors, accumulated during the last decade. He finds that the cure of cancer by radia-

tion results from the nice adjustment between injury to tumor cells resulting in necrosis, and injury to the surrounding tissue resulting in inflammation and repair. Dividing cells and rapidly growing tumors are usually more susceptible than others. A large part of the destructive effect of radiation is due to interference with the blood supply of the tumor through fibrosis of the vessels.

There are three methods of applying roentgen-ray therapy: the prolonged single exposure to a moderate dose, smaller fractionated doses repeated at frequent intervals and a single large and full exposure. The choice should be determined by the type of reaction desired: destruction of tumor cells or stimulation of the surrounding tissue. The effects of radium and roentgen rays also differ in this respect, the former acting chiefly on the tumor cells, the latter on the surrounding connective tissue. The general effect of the treatment on the body is also of much importance, improving the nutrition and metabolism, and possibly causing a nonspecific protein immunization which increases resistance to the tumor. A plea is made for more accurate histologic description of the effect of radiation on various tissues.

B. R. Lovett.

The Acute Changes in the Rabbit's Kidney, Particularly the Pelvis, Produced by Ligating the Ureter. Henry F. Helmholz and Ruth S. Field, J. Urol. **15**:409, 1926.

The changes in the pelvis consist of: (1) hemorrhage, edema and exudation of leukocytes which begin after four hours and reach a maximum in from eighteen to twenty-four hours; (2) destruction of small or large areas of the epithelial lining of the pelvis leading to ulcers or deep sterile abscesses in the peripelvic tissues; (3) healing beginning after forty-eight hours by the proliferation of connective tissue cells and the removal of the destroyed leukocytes by polyblasts; (4) healing of the small lesions of the pelvis by the formation of a pyogenic membrane and the lateral ingrowth of pelvic epithelium; (5) the formation of small diverticula by the action of the irritant urine when large openings have allowed the urine to reach far into the tissue; and (6) the replacement of the normal fat and connective tissue about the pelvis by dense fibrous connective tissue.

The changes in the kidney proper consist of: (1) exceptionally, focal necrosis of the epithelium with leukocytic infiltration; (2) very exceptionally (only once in this series), infarction of the kidney; and (3) necrosis of the tubules of the papilla, exceptionally with necrosis of the entire papilla.

The relation of these experiments to the pathology of pyelitis in man can be summarized as follows: (1) certain hemorrhages (evidence of which is found after death) in the pelvis of the kidney following obstruction of the ureters may be attributed to pressure and not necessarily to infection; (2) the formation of diverticula of the pelvis might give rise to a sterile pyuria that persists for a long time; (3) the products of acute inflammation can be removed so rapidly as to leave practically no trace after a period of fourteen days; and (4) the necessity of controlling results in experiments on the injection of bacteria into the pelvis when the ureter is obstructed, is evident; the presence or absence of infection makes no marked difference in the gross and microscopic appearance of hydronephrotic kidneys during the first twenty-four hours.

Accessory Spleen of Epididymis. I. M. Talmann, Virchows Arch. f. path. Anat. **259**:237, 1926.

In a Russian soldier, aged 22, pain in the left testis was associated with a palpable mass, the size of a hazelnut, in the head of the epididymis. The

diagnosis was tuberculosis of the epididymis, and orchidectomy was done. Microscopic examination proved the palpable tumor to be a small accessory spleen. A second, slightly smaller mass of spleen tissue was attached to the spermatic cord. The condition described was believed to be the result of embryonic misplacement of spleen tissue.

O. T. SCHULTZ.

PERIARTERIAL IRON AND CALCIUM INCRUSTATION OF SPLEEN. K. HENNINGS, Virchows Arch. f. path. Anat. **259**:244, 1926.

Hennings believes that the heavy deposition of iron and calcium which is seen not infrequently about the arteries of the spleen is the result of hemorrhage, which leads to the formation of hemosiderin. Following this there occurs a peculiar degeneration of the elastic and collagenous fibers of the artery wall and of the periarterial tissue, with infiltration of the degenerated fibers by calcium and hemosiderin.

O. T. SCHULTZ.

FAMILIAL OCCURRENCE OF MELANOSIS BULBI. E. M. SELTER, Monatschr. f. Kinderh. **31**:587 (March) 1926.

Pigmentation of the bulbar conjunctiva is rare in Europeans. It is more common in the dark races, mongolians and negroes. In Europeans, nevi of the conjunctiva occur, and also a more diffuse and atypical pigmentation, chiefly in the deep layers of the conjunctiva and the surface of the sclera. This anomaly is termed melanosis bulbi. Eighteen cases have been described. The author saw four cases in two generations of a European family. Three children and the father all had grayish blue spots in the sclera, chiefly along the blood vessels. There was no impairment of vision or other anomaly.

B. R. LOVETT.

ASSOCIATION OF PYELITIS AND NEPHRITIS. B. GOHRBANDT, Virchows Arch. f. path. Anat. **259**:269, 1926.

Gohrbandt tabulates sixty three cases of nephritis, varying from the acute purulent form to the chronic interstitial, in which he paid particular attention to pathologic changes in the pelvis of the kidney. In true inflammatory conditions of the kidney, pyelitis, usually of a subacute but sometimes of an acute form, was uniformly present. In the chronic renal conditions, the pelvis was also frequently the seat of subacute or chronic inflammatory changes. The author concludes that the relationship between the pelvis and kidney is so close that pyelitis without microscopic evidence of nephritis does not occur. The justification for this conclusion is not apparent, since the condition investigated was pyelitis secondary to nephritis rather than nephritis secondary to pyelitis.

O. T. SCHULTZ.

HEMATOPOIESIS IN THE ADRENAL MEDULLA. T. SSYSSOJEW, Virchows Arch. f. path. Anat. **259**:291, 1926.

In rabbits subjected to the blood destroying action of toluylendiamin, pyrogallol and other agents, the suprarenal medulla takes part in extramedullary hematopoiesis. In experiments in which aseptic foreign bodies (celloidin) were introduced into the suprarenal, the hematopoietic process was limited to the

medulla. The histiocyte of the reticulo-endothelial system is considered the stem cell which gives rise to large lymphocytes and hemocytoblasts, from which the various blood cellular elements are derived.

O. T. SCHULTZ.

ORIGIN OF MONOCYTES. K. PASCHKIS, Virchows Arch. f. path. Anat. **259**:316, 1926.

In his contribution to the controversy over the origin and nature of the large monocytes of the blood, Paschkis splenectomized rats which had been vitally stained with pyrrol blue. In nonsplenectomized vitally stained animals, no stained, large mononuclear cells appeared in the peripheral blood. In the splenectomized animals, monocytes with stored dye appeared on the sixth day after operation, and constituted about 2 per cent of the total leukocytes and 6.6 per cent of all the large mononuclear cells. The author concludes that the stained monocytes are of reticulo-endothelial origin, and thinks that his results help establish the trialistic doctrine of the origin of the blood cells. He believes that the unstained mononuclear cells have a similar origin to the stained ones, although admitting that his proof for these is not adequate.

O. T. SCHULTZ.

BLOOD CONTENT OF LIVER. W. SCHÜTZ, Virchows Arch. f. path. Anat. **259**:349, 1926.

Schütz determined the blood content of the liver by ligating the vessels before removal and then washing out all the blood from the vessels. Under normal circulatory conditions the blood constitutes 35 per cent of the total weight of the organ. In circulatory decompensation with chronic passive congestion the blood may make up 68 per cent of the weight of the liver. As fibrosis occurs the blood content decreases but still remains above the average for the normal liver, forming 46.8 per cent of the weight of the organ. In atrophic cirrhosis the blood content decreases out of proportion to the decrease in the weight of the liver, in terminal stages constituting only 10 per cent of the total weight.

O. T. SCHULTZ.

ENDARTERIAL NEW FORMATION OF VESSELS. H. BORCHARDT, Virchows Arch. f. path. Anat. **259**:373, 1926.

In two of twenty-four cases of gangrene of the lower extremity due to arteriosclerosis, Borchardt found new formed arteries within the obliterated lumen of the original artery. The walls of the new vessels contained smooth muscle and elastic tissue. These newly formed elements were believed to have arisen from indifferent mesenchyme as the result of the functioning of the new vessels. The author claims that there are no reported examples of a similar new formation of true arteries within obliterated vessels.

O. T. SCHULTZ.

HISTIOCYTIC REACTIONS IN ISOLATED RABBIT'S EAR. B. MALYSCHEW, Virchows Arch. f. path. Anat. **259**:379, 1926.

Malyschew perfused the isolated ear of the rabbit with Locke-Ringer solution in a water-bath at body temperature. The duration of the experiments was

from five to nine hours. Two hours after the perfusion was begun, living staphylococci in some instances and colloidal iron in others were injected subcutaneously or were added to the perfusing fluid. The perivascular histiocytes at some distances from the point of injection caused phagocytosis of the bacteria, but there was no phagocytosis at the point of injection. When the bacteria were introduced intravascularly, the pseudo-eosinophilous cells within the vessel lumen contained bacteria. The histiocytes stored the injected iron; the latter substance was present also in some of the cells of the epidermis.

O. T. SCHULTZ.

HISTOPATHOLOGY OF HYPOPHYSIS. H. KIYONO, Virchows Arch. f. path. Anat. **259**:388, 1926.

This is a casuistic study of changes in the hypophysis based on a large necropsy material, the exact number of hypophyses studied not being determinable from the article. The changes encountered are listed according to the portion of the organ involved. In the stalk there were found necrosis, leukocytic and lymphocytic infiltration, hemorrhage and tuberculosis, altogether nine cases. In the anterior lobe there were found four examples of necrosis, three of atrophy and one of ganglioneuroma. In a case of acromegaly the anterior lobe was enlarged, and eosinophilous cells were increased in number. In the pars intermedia there were found a cyst, much larger than the small colloid cysts so frequently seen, and ten cases of lymphocytic infiltration. Collections of neuro-epithelial cells in the posterior lobe were seen seven times. Especial attention was paid to the presence of epithelial cells and pigment in the posterior lobe in eighty-five cases, with positive findings in a large proportion. The epithelial cells are not believed to be misplacements of anterior lobe cells, but are derived from cells of the intermediate zone. The presence of pigment, believed to be proteinogenous in character, bears no relation to the epithelial cells. In a series of fourteen cases of mammary carcinoma, metastasis to the hypophysis occurred in 4 (21 per cent). The author does not believe that the adiposity sometimes seen in mammary carcinoma bears any relation to hypophysial metastasis.

O. T. SCHULTZ.

ON THE HISTOPATHOLOGY OF EXPERIMENTAL ACUTE POLIOMYELITIS (HEINE-MEDIN) IN MONKEYS AND GUINEA-PIGS. HANS GERHARDT CREUTZFELDT, Ztschr. f. Hyg. u. Infectionskrankh. **105**:402, 1925.

From a detailed study of the histology of the spinal cords of two monkeys (*Macacus rhesus*) and one guinea-pig, it is concluded that poliomyelitis was present in the guinea-pig whose source of infection might have been one of the monkeys previously injected with Heine-Medin virus; that the edema is of great importance in the course of the disease; that the leukomyelitis, setting in simultaneously with the nerve cell condition, is comparatively sparing of the long sensory tracts (dorsal fibers) and lasts longer; and that the neuronophagy in primates, according to strong histopathologic evidence, is accomplished not by leukocytes, but by glia cells (Hortega cells).

ETHEL B. PERRY.

Pathologic Chemistry

THE CALCIUM CONTENT OF THE BLOOD IN GOUT AND ARTHRITIS: PRELIMINARY REPORT. P. HOROWITZ, Am. J. M. Sc. **171**:560, 1926.

The blood calcium value, except in acute gout, whether during an attack or in an interval between attacks, is of no help in distinguishing gout from arthritis. The blood calcium concentration is normal or slightly higher in arthritis deformans and diabetes, below normal in arthritis complicated with otosclerosis or chronic nephritis, normal in chronic gout, and above normal in acute gout.

ARTHUR LOCKE.

BLOOD SERUM CALCIUM IN SPRUE AND OTHER PATHOLOGIC STATES IN THE TROPICS. B. K. ASHFORD and L. G. HERNANDEZ, Am. J. M. Sc. **171**:575, 1926.

Sprue develops, usually, as the result of nutritional disturbance and subsequent glandular insufficiency. The low serum calcium values are indicative of malnutrition rather than of specific disease and are better regarded in terms of parathyroid deficiency.

ARTHUR LOCKE.

URINARY PROTEINS: CRYSTALLINE PROTEINS OF NEPHRITIS. WILLIAM H. WELKER, WILLIAM A. THOMAS and LUDVIG HEKTOEN, J. A. M. A. **86**:1333, 1926.

In ten cases of nephritis, proteins were obtained in the form of globular crystals from the urine. In one instance, the protein appeared as needle-like crystals. Precipitin tests indicate that the protein crystals consist of compounds of serum albumin, euglobulin and pseudoglobulin.

THE INTRACUTANEOUS SALT SOLUTION TEST: ITS USE AS A TEST OF THE EFFICIENCY OF THE CIRCULATION IN THE EXTREMITIES. MILTON B. COHEN, H. S. APPLEBAUM and E. L. HAINSWORTH, J. A. M. A. **86**:1677, 1926.

The intradermal salt solution test is a rapid and accurate method of determining tissue affinity for water. Sixty minutes or more is the normal disappearance time. In all conditions associated with localized anoxemia, the salt solution disappearance time is decreased. In cardiac disease with decompensation, the disappearance time is always twenty minutes or less in the edematous areas. If there is no decompensation, normal values are obtained. In cases with peripheral arterial disease, the disappearance time is always decreased in areas showing clinical involvement. From observations in thirty-five cases, it has been noticed that readings below ten minutes have been found only in tissues immediately above areas of gangrene. Readings between ten and twenty-five minutes are strongly suggestive of developing gangrene.

AUTHORS' SUMMARY.

THE PHOSPHORUS CONTENT OF THE BODY IN RELATION TO AGE, GROWTH, AND FOOD. H. C. SHERMAN and E. J. QUINN, J. Biol. Chem. **67**:667, 1926.

The calcium intake is the limiting factor in the storage of both calcium and phosphorus in the body.

ARTHUR LOCKE.

CONCERNING THE RELATION OF GUANIDINE TO PARATHYROID TETANY. J. B. COLLIP and E. P. CLARK, J. Biol. Chem. **67**:679, 1926.

The urea and nonprotein nitrogen curves of untreated parathyroidectomized dogs are compared with those obtained following the injection of guanidine compounds. The results do not sustain the guanidine intoxication theory for the pathogenesis of parathyroid tetany.

ARTHUR LOCKE.

STUDIES ON THE INORGANIC COMPOSITION OF THE BLOOD. I. THE EFFECT OF HEMORRHAGE ON THE INORGANIC COMPOSITION OF SERUM AND CORPUSCLES. S. E. KERR, J. Biol. Chem. **67**:689, 1926. II. CHANGES IN THE POTASSIUM CONTENT OF ERYTHROCYTES UNDER CERTAIN EXPERIMENTAL CONDITIONS. Ibid., p. 721.

A single hemorrhage of from one third to one half of the total blood volume results in a slight decrease in the sodium and chloride contents of the serum. A greater decrease, together with an increase in inorganic phosphate, follows repeated severe hemorrhage. No change occurs in the potassium, calcium or magnesium content of the serum, but there is a large increase in the potassium content of the corpuscles.

The potassium content of the corpuscles is increased following insulin overdosage or subcutaneous injection of sodium oxalate. The increase is accounted for as an actual penetration of the potassium into the erythrocyte where it is stored in a nondiffusible form.

ARTHUR LOCKE.

CLINICAL CALORIMETRY: XLI. THE STORAGE OF GLYCOGEN IN EXOPHTHALMIC GOITER. H. B. RICHARDSON, S. Z. LEVINE and E. F. DUBOIS, J. Biol. Chem. **67**:737, 1926.

"The glycogen reserves of two patients with exophthalmic goiter were estimated to be at least as great as normal. This is evidence against the theory that there is any defect in the mechanism by which glycogen is stored."

AUTHORS' SUMMARY.

ANTIRICKETIC SUBSTANCES: III. THE CATALYTIC FORMATION OF AN ANTIRICKETIC CHOLESTEROL DERIVATIVE. C. E. BILLS, J. Biol. Chem. **67**:753, 1926.

An antiricketic substance of unknown nature is formed when a solution of cholesterol in carbon tetrachloride is boiled with activated fuller's earth.

ARTHUR LOCKE.

SUPRARENAL MELANODERMA. M. LOEPER, DECOURT and OLLIVIER, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:283, 1926.

It is concluded that melanin is an aminosulphurous substance. The suprarenals retain the sulphur; and therefore obliteration or removal of these glands increases the amount of sulphur in the organism. The high sulphur content of the blood with melanoderma suggests that it may be a factor in the pathogenesis of the pigmentation.

SERUM PROTEINS IN TEST DIURESIS. C. H. LASCH, Arch. f. klin. chir. **139**:419, 1926.

Lasch determined the total serum protein and the globulin fraction in blood taken before giving 1,500 cc. of water, four hours and twenty-four hours

afterward. The subjects fell into three groups: in group one, persons with good water excretion, the total protein increased while the globulin fraction decreased; group two, persons with poor water excretion, showed decrease in total protein with increasing globulin; group three, also with poor water excretion, showed increasing protein with decreasing globulin. All the fatal cases belonged to this group. The same changes as in group two are found after operations and irradiation. Investigators vary in their opinions whether the protein content can be used as a measure of the degree of concentration of the serum.

B. R. Lovett.

Critical Investigation of the Specificity of Histo-Chemical Methods of Fat Differentiation. C. Kaufmann and E. Lehmann, Centralbl. f. allg. Pathol. u. path. Anat. **37**:145, 1926.

The authors applied sudan, nile blue, Fischler, and Smith-Dietrich stains to fatty acids and a large variety of fatty substances and fat mixtures. They found saturation a factor in staining as unsaturated fatty acids took the stains much more readily than saturated fatty acids. The combination of components of a mixture was also important, for some mixtures remained unstained although their components singly took a stain. The results indicated the necessity for revising the textbook claims for the stains mentioned.

George Rukstinat.

The Significance of the Calcium and Thrombin for the Coagulation of Fibrin. E. Kaufmann, Klin. Wchnschr. **5**:453, 1926.

Plasma, dialyzed free from fibrin-ferments and calcium, may be clotted by the addition of gum preparations.

Arthur Locke.

The Calcium Content of the Cerebrospinal Fluid. F. Lickint, Klin. Wchnschr. **5**:556, 1926.

The determination of the concentration of calcium in the cerebrospinal fluid has little diagnostic value.

Arthur Locke.

Organic Iron Preparations. W. Heubner, Klin. Wchnschr. **5**:588, 1926.

Organic iron preparations are mainly dispersions of iron hydroxides made stable by an adsorption of the organic constituent. Such an adsorption markedly protects the iron-containing aggregate from disintegration and transition into the "inorganic" or ionized form. The iron preparations used in therapy may be classified as belonging to group A, preparations yielding ferrous iron; group B, preparations yielding ferric hydroxide; group C, complex compounds like hematin; group D, "active" forms such as exist in chalybeate springs and group E, mixtures.

Arthur Locke.

The Effect of Hunger on the Alkali Reserve in Human Blood. F. Walinski, Klin. Wchnschr. **5**:600, 1926.

The acidosis produced by hunger has its origin in the lowered carbon dioxide tension. This latter favors a displacement of fixed carbonic acid by stronger organic acids, with a consequent diminution of the alkali reserve.

Arthur Locke.

THE LIPOID THEORY OF NARCOSIS IN THE LIGHT OF RECENT INVESTIGATIONS. H. WINTERSTEIN, Klin. Wchnschr. **5**:642, 1926.

It may be that the scanty agreement between oil-dissolving power and narcotic strength should be regarded as accidental and the lipoid theory of narcosis discarded. The lipoids do not merely provide passive routes of transport, but participate intensively in the metabolism of the nerve centers. The burdening and possible alteration of the lipoprotein structures by the narcotic may play an important rôle in the production of narcosis.

ARTHUR LOCKE.

OXIDATION OF DIOXYPHENYLALANIN (DOPA) TO MELANIN. B. WALTHARD, Frankfurt. Ztschr. f. Path. **33**:141, 1925.

According to Bloch, the essence of pigment production is a specific ferment oxidation process by which a transformation of dioxyphenylalanin (dopa) to melanin takes place in the basal layers of the epidermis, the hair matrix, the nevus cell nests and in melanotic tumors. This reaction is due to the presence in these cells of an oxydase. Bloch and his students have shown that the autochthonous pigment in form, place and appearance is sharply differentiated from the usual chromatophores of the epidermis. The deep cutaneous melanoblasts of mongol spots, blue nevi and the hairy moles contain the pigment-forming ferment and give a positive "dopa reaction."

In his work, Walthard used either human or guinea-pig skin. The best results were obtained from freshly excised skin or that which had been fixed for only a short time in formaldehyde. Fixation for a period of two or three days does not injure the ferment. A positive reaction was obtained in specimens removed fifteen hours after death, but this was the upper limit.

To test for the reaction, pieces of skin are cut on the freezing microtome and the sections placed in distilled water. The 1 per cent dopa solution is diluted so that 2 mg. of dopa are contained in 2 cc. of pure, repeatedly distilled water. Some bound carbonic acid is freed by heating. To the boiled solution a buffer mixture of primary and secondary phosphates is added so that the H-ion concentration of the solution is 7.3 to 7.4 which is the optimum for the reaction. This mixture is placed in a scrupulously clean glass dish and the frozen sections placed therein and allowed to remain for twenty-four hours at room temperature or for from five to ten hours at 37 C. After the reaction is complete the sections, which may be counterstained by methyl green-pyronin, are passed through alcohol and xylol and mounted in balsam.

A positive reaction is indicated by the appearance of dark, usually black, spots in the basal cells; these spots often together form a streak or band. All variations in the intensity of the reaction exist according to the condition of the basal cells, ranging from smoky gray to deep black. Bloch made out two kinds of dopa-positive cells or melanoblasts; cylindric cells somewhat obscured by the reaction, and dendritic cells which lie between the basal cells.

The nuclei of the cells do not react. The sweat and sebaceous glands and the chromatophores of the cutis show no reaction. The cells of the hair matrix, on the other hand, react so strongly that often their outlines cannot be made out. In the spotted skin of the guinea-pig where there is increased pigmentation there is also an increased number of melanoblasts. On the other hand, a skin may contain much pigment as in the lower extremities of old people and yet give a negative or very weak dopa reaction. This is because the pigment production has long since ceased and no specific pigment is present.

Melanotic pigment and pigment from the eye and dura mater give a negative dopa reaction. However, during the formation of the choroid pigment the reaction is positive, and if a melanotic tumor develops in the eye, the reaction is positive.

Walthard demonstrated experimentally that the dopa-reaction is not stimulated when other chemical substances are used such as tyrosin, epinephrine, dimethyl- and paraphenylenediamin, etc. He contends that the reaction is an oxyadase reaction whose rate increases with the rise in temperature within a given range. Short heating destroys the ferment.

In a case of pigmentation of the colon the dopa-reaction was negative thus indicating that the pigment was not melanin. A case of pigmented nevi and a case of a melanotic tumor of the skin both gave positive reactions. Walthard believes with Bloch that a positive reaction in these cases indicates a close correlation between the nevi and tumor cells with the basal cells of the epidermis and that these tumors have an epithelial origin.

E. M. Hall.

The Prognostic Value of the Colloidal Gold Reaction in Meningitis. T. Falkiewicz, Ztschr. f. d. Nervenh. **89**:299, 1926.

Cases are cited to show that in meningitis, peaks at the beginning and end of the gold curve are associated with a fatal ending. It is concluded that such a curve found during the course of a meningitis means death shortly.

Roy Grinker.

The Insulin Complement. C. Lundsgaard and S. A. Holböll, Ugesk. f. Laeger **88**:106, 1926.

This term insulin complement is proposed by Lundsgaard and Holböll for the active substance or principle in muscle tissue which, when finely divided muscle tissue is added to insulin in vitro and placed in contact with a solution of glucose, transforms alpha and beta glucose into the form which they call "new glucose." Neither alone can accomplish this transformation; it requires the combination of both muscle tissue and insulin.

The Insulin Complement. C. Lundsgaard and Others, Ugesk. f. Laeger **88**:273, 1926.

Further research on the element in muscle tissue which, associated with insulin, transforms alpha and beta glucose into neoglucose, shows that it is not identical with Meyerhof's muscular coferment. It cannot be obtained from muscle tissue by water extraction, and it does not stand heating to 70 C. for two minutes. As its presence cannot be demonstrated in the juice obtained by pressure from muscle tissue, the insulin complement must be bound to the intact cell. It is found in both cold-blooded and warm-blooded animals.

Microbiology and Parasitology

The Effects of Atmospheres Rich in Oxygen on Normal Rabbits and on Rabbits with Pulmonary Tuberculosis. A. L. Barach, Am. Rev. Tuberc. **13**:293, 1926.

Rabbits kept in an atmosphere containing more than 60 per cent of oxygen died of pneumonia or pulmonary edema. A concentration of 60 per cent is not

harmful but has no appreciable effect on the evolution of pulmonary tuberculosis in rabbits. Tuberculous rabbits treated in this way in the majority of cases survived their untreated controls, but no specific influence on the pathologic anatomic changes were observed. The increased duration of life in the treated animals is explained chiefly by the prevention of death by anoxemia and by the diminished pulmonary excursions.

MAX PINNER.

THE BACTERICIDAL ACTION OF ULTRAVIOLET LIGHT ON THE TUBERCLE BACILLUS. H. H. HOWZE, Am. Rev. Tuberc. **13**:470, 1926.

A suspension of virulent human tubercle bacilli exposed for five minutes to a standard mercury quartz lamp at a distance of 10 inches did not produce any tuberculous lesions in guinea-pigs within thirty-five days after subcutaneous injection.

MAX PINNER.

HOG CHOLERA STUDIES. R. A. WHITING, J. Infect. Dis. **38**:256, 1926.

The results of exposures to hog cholera, made outdoors during the summer seasons, show that hog cholera is easily transmitted over short distances. However, when the distance approximates that of the average width of farm lanes, the disease is not easily transmitted. Similar occurrences have been observed in field outbreaks.

The results of exposures made indoors during the winter seasons show that hog cholera can be transmitted consistently across small spaces regardless of ordinary pen partitions and without direct contact also that such transmissions can be prevented by placing a cheese-cloth curtain between the pens.

Hog cholera virus was viable in closed pens two days after the removal of sick and dead cholera hogs. The virus also remained alive in grass yards for two days during the month of November, and for one day during the hot weather of summer. However, in both cases only one of four pigs developed the infection, indicating that pigs may escape picking up infection in large yards.

Mixtures of sterile soil with blood, feces and urine of hogs with cholera were dried at room temperature for six days. The blood and soil mixtures remained virulent for five days. With possibly one exception, the feces soil and the urine soil mixtures were not virulent twenty-four hours after being removed from the bodies of hogs with cholera.

Fresh urine and feces were virulent at different periods after inoculation. There are indications that the feces become virulent before the urine, and that the virulence of the urine persists longer than that of the feces.

Pigs developed hog cholera when exposed to dry straw bedding on which blood had been sprinkled five days previously.

Blood dried from one to fifteen days at room temperature proved to be virulent when fed or injected.

Eye secretions dried under the same conditions were virulent from one to thirteen days. In one instance, eye secretions proved to be virulent after fifteen days of drying.

Skin scrapings dried eight days were also virulent when fed and injected, but did not produce cholera after nine days of drying.

AUTHOR'S SUMMARY.

A Comparative Study of Strains of Clostridium Chauvoei Obtained in the United States and Abroad. Joseph P. Scott, J. Infect. Dis. **38**:262, 1926.

A review of previous work indicates that *C. chauvoei* is the primary cause of blackleg in cattle. *C. oedematis* and other anaerobes may be associated with it.

Pathogenicity tests show that *C. chauvoei* is highly pathogenic for cattle, but that injections of *C. oedematis* and *C. novyi* are nonpathogenic for these animals.

Filtrates and muscle extracts from cases of blackleg caused by typical *C. chauvoei* cultures are shown to be nontoxic. *C. chauvoei* does not produce a soluble exotoxin.

Biologic products made from pure nontoxic strains of *C. chauvoei* are shown to be highly efficient, while toxic products and those made from atypical products are of little or no value.

Strains obtained from California, Scotland, France, Germany, and Switzerland are shown to be identical with the Kansas type strains. Reports from other workers indicate that the organisms causing La Mancha in Argentina, Manqueira in Brazil and blackleg in South Africa and Australia are also the same.

Four strains of *C. chauvoei* obtained from different sources are shown to be atypical.

C. chauvoei is shown to be a different saccharolytic organism fermenting glucose, lactose and sucrose under favorable conditions. *C. oedematis* is seen to be a vigorous saccharolytic organism which ferments all sugars under favorable conditions, but under adverse conditions ferments only glucose, lactose and salicin. *C. novyi* is shown to blacken unfiltered gelatin.

The agglutination reactions correspond fairly closely with the fermentation reaction tests.

From a study of the pathogenicity tests, the immunization tests and field use of blackleg aggressin and filtrate produced from typical strains, it is suggested that the inclusion of atypical strains, *C. oedematis* strains or intermediate types, while being theoretically advisable, would not increase the efficiency of the pure products to any appreciable extent. The use of about 250,000 doses of blackleg filtrate and of several million doses of blackleg aggressin produced from Kansas type cultures has been followed by a loss of less than 1 in 10,000. These products have been used successfully in all parts of the United States and in Central America, Argentina and South Africa.

Authors' Summary.

Observations on Castellani's Fermentation Phenomenon. Juan Manuel Fiallos, J. Trop. Med. **28**:426, 1925.

The experiments confirm Castellani's work. The phenomenon he has described is the following: Two bacilli, neither of which causes production of gas in certain carbon compounds, may do so when artificially mixed together, provided one of them is capable of producing simple acidity (never gas) in those carbon compounds and the other, though inert on those carbon compounds (namely, does not produce in either of them acidity or gas) is capable of producing gas in glucose.

For example, *Bacillus typhosus* never produces gas, only simple acidity in maltose, mannitol and sorbite; *B. morgani* alone is inert on those substances, namely, does not produce either acidity or gas; their mixture, however, produces gas, although one would expect that by adding to a germ which produces simple

acidity, a germ which produces neither acidity nor gas, there would still be only production of simple acidity.

Similarly, neither *B. dysenteriae Flexner* nor *B. proteus* (P) produce gas in mannitol; the first produces only simple acidity and the other is inert; their mixture, however, produces acidity and gas.

AUTHOR'S SUMMARY.

A MORPHOLOGICAL AND CULTURAL INVESTIGATION OF VIBRIOTHRIX ZEYLANICA CASTELLANI. MARIO PERUZZI, J. Trop. Med. **29**:44, 1926.

A strain of *Vibriothrix zeylanica* (Castellani) was isolated in the autumn of 1923 at Pola from soldiers affected with bacillary dysentery.

Staining with Giemsa's method puts in evidence the complex structure of this micro-organism, and shows the presence of a nuclear apparatus highly differentiated, which plays a rôle in the phenomena of reproduction.

V. zeylanica is an extremely polymorphic organism with vibrio-like, bacillus-like, spirillum-like, coccus-like and filamentous and large globose forms. The cultures obtained in broth-blood are filtrable through Berkefeld N. candles.

The intraperitoneal injection of massive doses causes death in guinea-pigs, while the injection of ordinary doses does not cause death, and the organism is destroyed by a process of leukocytosis. With regard to the classification of the organism, the presence of branching filaments and sporiform bodies is in favor of the organism belonging to the *Fungi imperfecti;* the rapid growth, the presence in certain mediums of only bacillary forms and vibrioforms, its antigenic and immunizing action might be reasons to place it among the bacteria; the spirochetic elements and the well marked morphologic and chromatic differentiation of the nuclear apparatus are suggestive of protozoal forms.

Owing to these various morphologic characters, the systematic position of this micro-organism could not be better defined than by the new genus *Vibriothrix* created by Castellani.

AUTHOR'S SUMMARY.

AVIAN TUBERCULOSIS IN MAN. C. H. MAYO and W. A. HENDRICKS, Southern M. J. **19**:29, 1926.

Two cases diagnosed as avian tuberculosis are reported. One occurred in a woman, aged 26, who had a secondary anemia with a low color index and a moderate lymphocytosis; there was no free hydrochloric acid in the stomach. She had painful menstruation, febrile temperature and an enlarged spleen. The second case was in a woman, aged 22, who suffered pains beneath the lower end of the sternum after eating; there was a splenic tumor, normal temperature and secondary anemia. In both cases the spleen, which was nodular, was removed, and the livers were covered with small yellow areas. Both patients recovered. The pathologic anatomic diagnosis is based on the scarcity of giant cells, and on the fact that many tubercles are not caseated but show in the center "large epithelioid cells in great numbers, which give a characteristic appearance to the avian lesion, in contrast to that of human and bovine tuberculosis."

These two cases do not show the clinical characteristics of previously reported cases of avian tuberculosis (see Löwenstein, Ztschr. f. Tuberk. **41**: 18, 1925), namely, polycythemia or leukemia and predilection for renal localization besides splenic tumor and hepatic involvement. It is not mentioned whether the foci contained acid-fast organisms, although the enormous number of acid-fast rods in the foci is the most significant differentiating mark from human

or bovine infections. Whether the mere histologic structure of the tubercles permits of a definite diagnosis appears doubtful from the work of previous investigators. It is felt that only bacteriologic methods, including pure cultures and animal inoculations, justify a diagnosis as to the type of acid-fast organisms.

MAX PINNER.

THE PATHOGENIC ACTION OF A COMMA-LIKE VIBRIO IN THE GUINEA-PIG. DANTE DE BLASI, Ann. d'ig. **36**:1, 1926.

A strain of the vibrio comma was isolated from a well which was almost identical with the true cholera vibrio. No morphologic or cultural differences existed. The organism, however, was not agglutinated by anticholera serum and was pathogenic for the guinea-pig. Transplantations and passage through animals did not change its inagglutinability. Injected into the peritoneal cavity of the guinea-pig, it rapidly traversed the lymphatic channels, particularly the epiploic processes, entering the circulation. Localization then followed in the intestinal wall, where it was disposed off or produced a lesion. It showed a marked enterotropism. The course of its localization is the same as that described by Sanarelli for the typical organism.

E. E. ECKER.

THE ACTION OF THE ORGANISM ON THE VITALITY OF GERMS EXPELLED THROUGH THE INTESTINAL TRACT. G. PERGHER, Ann. d'ig. **36**:81, 1926.

Spores of glycobacteria were used to study the elimination of nonpathogenic organisms by the intestines. Following intratracheal injection, the spores were found to be absorbed into the blood stream rapidly. Later they were recovered from the liver, spleen and lower intestinal tract. There were none in the duodenum, the bile was sterile, and the largest number were found near the ileocecal valve. They could be demonstrated in the succus entericus. During their passage through the respiratory apparatus to the intestinal tract, the germs underwent attenuation in their vitality. Spores recovered from the intestinal juices were shown to be less resistant to heat than others.

B. R. LOVETT.

ORTHOSTATIC HEMOGLOBINURIA, HEMOLYTIC ICTERUS, URINARY AMEBIASIS, CURE BY EMETIN. NOËL FIESSINGER and GASTON PARTURIER, Bull. et mém. Soc. med. d. hôp. de Paris **42**:153, 1926.

A man, aged 25, developed attacks of orthostatic hemoglobinuria some time after an attack of dysentery. The hemoglobinuria had none of the characteristics of the paroxysmal form—there was no hemolysin in the blood and no increased fragility of the corpuscles; the icterus was purely hemolytic. The spleen was enlarged. The hemoglobinuria was relieved fairly promptly by complete rest. After a time, *Amoeba histolytica* was demonstrated in the urine, and the treatment with emetin resulted in cure.

The authors cite several reports of urinary amebiasis, mostly characterized by cystitis, sometimes associated with hematuria, and in some cases associated with nephritis. Their case is peculiar in that there was an orthostatic hemoglobinuria without any obvious infectious relations except amebas in the urine.

L. HEKTOEN.

HUMAN TUBERCULOSIS AT DIFFERENT AGES. TUBERCULOSIS OF SENESCENCE, W. BLUMENBERG, Beitr. z. klin. Tuberk. **63**:13, 1926.

These studies were made on 125 persons, 60 or more years of age at death. Healing of thoracic tuberculosis becomes more frequent with increasing age. The localization of the primary complex is the same as in younger persons. The elastic fibers of the primary focus are less preserved in very old patients, and its fibrotic capsule is more marked. Primary complexes which originated during senescence show little glandular involvement. The foci of reinfection are mostly multiple, and favor the central parts of the upper lobes, not the apexes. Bronchogenic dissemination is the rule; hematogenic dissemination becomes rarer with increasing age. Tuberculosis of the serous membranes, the larynx and the intestines is frequent; the tonsils are less frequently involved. The peculiarities of tuberculosis in old age are not dependent on immunizing factors.

As result of his entire studies, the author emphasizes the following points: the rule that invading tubercle bacilli always cause pathologic changes at the site of entrance (Baumgarten-Tangl) holds good for thoracic tuberculosis, not for abdominal infections. Tubercle bacilli may pass the intestinal wall and cause a primary tuberculosis of the mesenteric lymph glands without producing any changes in the intestinal mucosa; but this seems to occur in childhod exclusively. Parrot-Cornet's rule, according to which the regional lymph glands of the primary focus always undergo caseation, is true only for childhood. With increasing age the lymph glands show only partial caseation and finally only the formation of cellular tubercles. The anatomic structure of the pulmonary primary focus (caseous hepatization) and its subpleural localization is the same at all ages; it is mostly singular and has a tendency to more apical localization at higher ages; transformation into a small cavity is frequent. Hematogenic dissemination, besides lymphogenic and bronchogenic, is the rule and only in old age is slightly less frequent. Indurative processes are not found during the first year of life; they become more frequent with increasing age. Careful anatomic studies do not lend any support to the generally accepted opinion that a process of immunization modifies the evolution of a tuberculosis, but emphasizes that age is the most important factor to explain the peculiarities of tuberculosis in infancy, childhood, adult life and old age.

MAX PINNER.

PATHOLOGIC-ANATOMIC CHANGES IN THE TESTICLES IN PULMONARY TUBERCULOSIS. W. J. ROSCHDOSTRONSKY, Beitr. z. klin. Tuberk. **63**:138, 1926.

Studies on thirty cases showed that a tuberculous toxemia of long duration always produces atrophic changes in the regenerative tissue of the testicle and hypertrophic changes in the interstitial tissue.

MAX PINNER.

EXPERIMENTS ON THE FILTRABLE TUBERCULOUS VIRUS. A. FESSLER, Centralbl. f. Bakteriol. I. O. **98**:148, 1926.

The author tried in several series of very carefully planned experiments to duplicate the results of Fontes, Vaudremer and Valtis and their co-workers on the filtrable virus in tuberculosis. He was in no case able to cultivate from the filtrates of tubercle bacillus cultures or of tuberculous tissue the atypical bacilli described in the work of the French authors, nor did he succeed in

infecting animals with such filtrates. He believes that in their work contaminations may account for the pathologic changes obtained in guinea-pigs, and he considers the possibility that splitters of the tubercle bacillus (Spengler) may pass the filter.

MAX PINNER.

INFECTION WITH THE VIRUS OF HERPES AND IMMUNITY IN GUINEA-PIGS. G. ROSE and B. WALTHARD, Ztschr. f. Hyg. u. Infektionskr. **105**:645, 1926.

Rose and Walthard have made a careful investigation of various forms of infection with different strains of the virus of herpes in guinea-pigs and have determined how much immunity is produced by a first attack of the disease in these animals. They confirm previous observations to the effect that a typical kerato-conjunctivitis follows the infection of the cornea of guinea-pigs with this virus. It runs a much shorter course than that experimentally produced in the rabbit and heals completely even in severe cases. No signs of general infection were ever observed after this form of inoculation. Encephalitis may develop after subdural injection of the virus in guinea-pigs, but it does not do so with the same regularity as in rabbits. The resistance of the brain in guinea-pigs is great. In their series the authors did not observe one case of fatal encephalitis after corneal inoculation. By intracutaneous injection they succeeded in infecting the hairy parts of the skin in guinea-pigs. The reaction consisted in the development either of typical herpes vesicles, single or multiple, or of an atypical infiltration usually followed by central necrosis. The character of the reaction seemed to depend to some extent on the nature of the virus used. The hairless part of the paws of the guinea-pigs can also be succeesfully infected, but even with the most virulent strain the result was negative or doubtful in 10 per cent of the inoculated animals. This form of inoculation may be followed by signs of a myelitis in the lumbar region. The animals show a flaccid paralysis of the hind legs which may be followed by paralysis of the sphincters of rectum and bladder. No reliable method is available to ascertain the presence or absence of sensory disturbances, but it is probable that such are present because the animals often expose their paralyzed limbs to trauma and even bite them until they bleed. If one side only is infected, both legs may be paralyzed. The most active strain of virus produced paralysis of the extremities in 77 per cent and of the bladder and rectum in 58 per cent of the animals which had been inoculated on the soles of their hind legs. The severity of the myelitis varies very much in different cases. It does not show any tendency to spread upward. Recovery is usually complete clinically. Only one animal was still partly paralyzed after five months, when it was killed in order to make a microscopic examination of the cord. A microscopic study of the spinal cords of the animals with successful plantar infection revealed the presence of myelitis even in those which did not show any clinical signs of it. The infection follows the course of the ischiadic nerve and is most marked posteriorly in the region where the roots carrying its nerve fibers arise from the cord. The pia on the posterior surface and the white and gray substance posteriorly are congested and heavily infiltrated with round cells. There may be areas of necrosis. The motor ganglion cells in the anterior gray columns are not seriously affected with few exceptions even in the paralyzed animals, which explains the possibility of complete recovery. The lesion heals with the development of scar tissue in the posterior pia and in the affected parts of the gray and white substance. In the animal with apparently permanent paralysis, there was scarring in the anterior gray columns also. All doubt of the herpetic nature

of the myelitis was removed by positive inoculation experiments with material obtained from the diseased cord. After the subsidence of the first infection no complete immunity remains but a second infection of the cornea, or the hairy skin or the plantar surface runs a milder course. A reinfection of the spinal cord was not observed in any of the animals tested by reinfection of the plantar skin. These experiments on guinea-pigs confirm the neurotropic character of the virus and demonstrate that an infection of the cord occurs with unexpected constancy after inoculation of the soles of the hind legs. The authors believe that the possibility of producing a localized myelitis with spontaneous recovery may be of general neurologic interest. Further experiments along these lines may also shed some new light on the relations between the virus of herpes and that of poliomyelitis.

W. Ophüls.

Immunology

Effect of Certain Substances on the Precipitin Reaction. Cornelia M. Downs and Kenneth Goodner, J. Infect. Dis. **38**:240, 1926.

The presence of an heterologous protein, such as normal serum, does not interfere with the precipitin reaction or intensify the prozone, thereby confirming Nuttall's results on the specific solubility of the precipitate in the homologous antigen. Heterologous proteins did, however, cause dissociation of the formed precipitate.

A solution of the precipitate in weak carbonate was shown to contain active precipitinogen but no precipitin.

On neutralization of the carbonate extract, both precipitinogen and precipitin were readily demonstrable.

Concentrated solutions of dextrose and saccharose inhibit the formation of precipitate in the precipitin reaction.

Dextrose dissolves the precipitate and apparently causes a true dissociation, since both precipitin and precipitinogen can be demonstrated in the extraction fluid from the washed precipitate.

Saccharose has no dissolving effect and causes only slight dissociation of the formed precipitate.

Other carbohydrates seem to interfere little with the precipitin reaction and act as weak dissociating agents, but they were not used in the same high concentration as the dextrose and saccharose because of lack of solubility.

Authors' Summary.

The Influence of the Size of the Inoculum on the Incubation Period and Course of Rabbit Syphilis. George E. Wakerlin, J. Infect. Dis. **38**:323, 1926.

The number of *Spirochaetae pallidae* in the inoculum influences the incubation period of experimental rabbit syphilis. The smaller the number of infecting organisms, the longer is the incubation period.

The number of spirochetes in the inoculum does not appreciably affect the subsequent course of the disease, inclusive of the Wassermann reactions.

Author's Summary.

WASSERMANN REACTION IN RABBIT SYPHILIS. G. E. WAKERLIN and P. H. CARROLL, J. Infect. Dis. **38**:327, 1926.

The Wassermann reaction in rabbit syphilis is an index of tissue-spirochete interaction and is not a criterion of the presence or absence of the spirochete.

The Wassermann reaction is consistently positive in about 99 per cent of the cases of active rabbit syphilis following intratesticular inoculation.

The appearance of the positive Wassermann reaction in rabbits affected with syphilis may be completely suppressed by the institution of adequate treatment in the clinically active but prepositive Wassermann stage.

AUTHORS' SUMMARY.

STUDIES ON ANTHRAX IMMUNITY. I. THE ATTENUATION OF BACILLUS ANTHRACIS BY MEANS OF SODIUM CHLORIDE AND OTHER CHEMICALS. S. J. SCHILLING, J. Infect. Dis. **38**:341, 1926.

It was found that sulphuric acid and copper sulphate hydrolyze agar when added to this medium, even in such dilute concentrations as would not be expected to inhibit growth of *B. anthracis*.

The addition of 4.5 per cent sodium chloride and the addition of 1 per cent potassium ferrocyanide to standard agar appears to represent about the maximum concentration of these chemicals which may be used without completely inhibiting the growth of the anthrax bacillus. The growth-inhibiting concentration of sodium hydroxide is about 0.15 per cent.

An increased tolerance to sodium chloride, potassium ferrocyanide and sodium hydroxide could be noticed in successive transfers of the anthrax bacillus, as judged by the production of a more luxuriant growth.

After growing the anthrax bacillus for seven weeks on agar containing 1 per cent potassium ferrocyanide, and for the same length of time on agar containing 0.15 per cent sodium hydroxide and testing the culture by inoculating guinea-pigs, no decrease in virulence of the organism could be detected.

After growing the anthrax bacillus for six weeks on agar containing 5 per cent sodium chloride, marked attenuation of the anthrax bacillus was demonstrated by gunea-pig and rabbit inoculation.

Attempts to immunize guinea-pigs with the sodium chloride attenuated culture failed. Presumably this was because sufficient intervals of time were not permitted to elapse between injections.

It was found that rabbits could be successfully and safely immunized by the use of the culture attenuated by growing on 5 per cent sodium chloride agar, so that they withstood the injection of virulent cultures of the anthrax bacillus in quantities which are regularly fatal to normal animals.

AUTHOR'S SUMMARY.

AGGLUTINATION OF TUBERCLE BACILLI. SLIWENSKY, Beitr. z. Klin. d. Tuberk. **62**:282, 1925.

Technic: Four cubic centimeters of a 1 per cent salt solution are mixed with 0.4 cc. of a bacillary suspension; after one hour 0.2 cc. of serum are added; incubation for twenty-four hours. The agglutination takes place at the

surface of the mixture. Of sixty-nine tuberculous patients, 72 per cent reacted positively; 48 control patients reacted negatively. The best results were obtained with a suspension of avian tubercle bacilli.

MAX PINNER.

COMPLEMENT-FIXATION IN TUBERCULOSIS WITH BESREDKA'S ANTIGEN IN EXUDATES. K. MICHAILOW, Ztschr. f. Tuberk. **43**:191, 1925.

The complement-fixation reaction in pleural exudates yields diagnostically reliable results; it is in full agreement with the bacteriologic and cytologic observations. A positive test is believed to prove the existence of a tuberculous focus.

MAX PINNER.

TUBERCULIN ALLERGY AND TUBERCULIN ACTION. H. SELTER, Ztschr. f. Tuberk. **45**:11, 1926.

On the foundation of extensive experimental work both on animals and on man, Selter draws the following conclusions: Tuberculin allergy is an increased capacity of the tissues to respond to certain stimuli with an inflammatory reaction. One of these stimuli is in contact with tuberculin, but other materials may cause the same response clinically, histologically and biologically. The tuberculin reaction, therefore, is no antigen-antibody reaction; this is supported by the fact that old tuberculin injected into normal animals does not produce complement fixing antibodies or produces them only to a slight degree.

Tuberculin allergy may develop in either of two ways: either intestinal bacteria may produce an increased inflammatory reactivity, which is increased by a subsequent tuberculous infection; or only the tuberculous infection may produce the allergy. In any event, a positive tuberculin reaction may demonstrate a nonspecific state of allergy; and in the course of a tuberculous infection nonspecific stimuli may simulate perfectly a typical tuberculin reaction.

MAX PINNER.

BLOOD GROUPS IN MOTHERS AND CHILDREN. V. OHNESORGE, Zentralbl. f. Gynec. **49**:2884, 1925.

Ohnesorge's data include 302 women and 250 children (including nine pairs of twins). The congruence or incompatibility in the blood groups in mother and child seems to have no connection with the development or sex of the child nor with the toxicoses of pregnancy. He tested the corpuscles from ten fetuses of the fourth to the sixth month. There was no agglutination in seven cases. Two fetuses of the fourth and one of the fifth month belonged to group II.

ATTEMPTS AT PRODUCING ALLERGY AND IMMUNITY IN GUINEA-PIGS BY INJECTION OF KILLED TUBERCLE BACILLI. Ztschr. f. Hyg. u. Infectionskrankh. **105**:571, 1925.

The production of skin allergy in normal guinea-pigs can be induced by heat killed tubercle bacilli introduced by the intracutaneous, subcutaneous, intraperitoneal and intravenous routes. The results are irregular; the most reliable methods appear to be the intradermal or intraperitoneal injections. Occasionally a positive skin test is obtained in animals that received intracutaneous injections of killed *B. coli* and old tuberculin.

MAX PINNER.

Tumors

THREE TUMORS ARISING FROM NEUROBLASTS. W. BOYD, Arch. Surg. **12**:1031, 1926.

Three more cases are added here to the rapidly growing list of tumors usually found in young children, now known to arise from the primitive nerve cell, and nearly always from the sympathetic nervous system. The cases here reported include one from the suprarenal medulla, one from the abdominal sympathetic and the third from the retina. The mechanism of metastatic spread is discussed.

N. ENZER.

THE OCCURRENCE OF CHORIOANGIOFIBROMA (CHORIOANGIOMA). A STUDY OF SIX HUNDRED PLACENTAS. R. S. SIDDALL, Bull. Johns Hopkins Hosp. **38**:355, 1926.

Six small angiofibromas of the chorea were found in 600 placentas.

OBSERVATIONS ON THE ETIOLOGY OF TUMORS AS EVIDENCED BY EXPERIMENTS WITH A CHICKEN SARCOMA. JAMES B. MURPHY, J. A. M. A. **86**:1270, 1926.

Anaerobic "cultures" of chick embryo and rat placenta have proved just as effective as so-called cultures of malignant tumors in activating chloroform treated filtrates of a chicken sarcoma. The necessity of assuming a cultivated living organism in the interpretation of Gye's results is eliminated.

AUTHOR'S SUMMARY.

ON THE DIALYSABILITY OF THE GROWTH-ACTIVATING PRINCIPLE CONTAINED IN EXTRACTS OF EMBRYONIC TISSUES. G. PAYLING WRIGHT, J. Exper. Med. **43**:591, 1926.

These experiments appear to indicate that whatever substance in embryonic tissue extracts excites mitosis, and therefore would appear to be the growth-stimulating substance, is capable of passing through a collodion membrane which is impermeable to proteins, at all events in such concentration as would give rise to any biuret reaction. The substance is therefore diffusible.

AUTHOR'S SUMMARY.

SOME CONDITIONS OF THE REPRODUCTION IN VITRO OF THE ROUS VIRUS. ALEXIS CARREL, J. Exper. Med. **43**:647, 1926.

It is concluded that the reproduction in vitro of the active virus depends on the presence of fresh tissues in the culture and on the quantity, the activity and the nature of the cells contained in the medium.

AUTHOR'S SUMMARY.

CHANGES IN THE REACTION POTENTIAL OF A TRANSPLANTABLE TUMOR. LEONELL C. STRONG, J. Exper. Med. **43**:713, 1926.

Mutations or hereditary genetic changes may occur within the tumor cell at least during the process of transplantation. These mutations may explain the phenomenon of the change in the reaction potential and deviations in the proliferative vigor of the tumor cell during the process of transplantation. The nature of this mutational process is as yet undetermined. The phenomenon

of tissue specificity is determined to a large extent at least by the genetic constitution of the neoplastic tissue. The tumor mass may deviate from the genetic constitution of the host tissue that gave rise to it, at least during the process of transplantation.

AUTHOR'S SUMMARY.

VIABILITY OF DESICCATED OR GLYCERINATED CELLS OF A CHICKEN SARCOMA. W. NAKAHARA, Science **63**:549, 1926.

Three methods have been used to demonstrate the existence of the assumed agent of chicken sarcoma, which is regarded as separable from sarcoma cells, namely, filtration, desiccation and glycerolation. It has been taken for granted that these processes either completely eliminated or killed the cells, leaving the caustive agent viable. Judging from the fact that mammalian neoplasms have occasionally been transmitted by the Berkefeld filtrates it is doubtful whether the filtrability alone can be accepted as conclusive evidence. If desiccation or glycerolation does not kill the sarcoma cells, as the experiments here reported indicate, the question of a causative agent, separable from the cells, would seem to require careful reconsideration. The remarkable viability of the sarcoma cells demonstrated in Nakahara's experiments should be of significance in the study of the nature of avian new growths.

THYROID METASTASIS TO BONE, WITH A DISCUSSION OF SO-CALLED "BENIGN METASTASIZING GOITER." W. M. SIMPSON, Surg. Gynec. Obst. **42**:489, 1926.

Three cases of osseous metastasis of thyroid tissue are reported. At the time of admission each patient presented symptoms directing the clinicians' attention chiefly to the bone tumors. The first was a case in which spontaneous fracture of the femur occurred as a result of the presence of a tumor composed of histologically benign thyroid tissue. A small goiter gave no evidence of malignancy. In the second case, the metastasis was in the astragulus. Again the microscopic picture was that of typical thyroid tissue, and the patient possessed a small, symmetrical goiter which was regarded as benign clinically. The third patient presented signs of vertebral neoplasm with compression myelitis, but with no clinical signs which might direct suspicion to the thyroid gland. Laminectomy exposed a hazelnut-sized tumor in the sixth cervical vertebra, which on microscopic examination contained areas of typical thyroid tissue. All these patients later developed unmistakable clinical evidence of malignancy of the thyroid gland, and all died within a year and half following operation. The author reviews seventy-seven cases collected from the literature which were reported as examples of "benign metastasizing goiter," and attempts to prove that there is no such entity. He analyzes the first case described by Cohnheim in 1876 and demonstrates evidences of malignancy in that, showing the fallacy that metastasizing goiters are benign.

M. L. PARKER.

GENERAL RELATION OF CARCINOMA TO ULCER. MATTHEW J. STEWART, Brit. M. J. **2**:882, 1925.

During fifteen years at Leeds, where 7,930 necropsies were performed, Stewart found that there were 165 cases of carcinoma of the stomach, that the majority occurred between the ages of 40 and 70 years, the youngest patient being 18, the eldest 76, and that there was a preponderance in males of 2 to 1. In discussing the question of the relation of ulcer to cancer, he believes that when

one does not find muscle tissue in the floor of the cancerous depression, it probably originated in an ulcer that was chronic; when muscle tissue is found, it probably developed without previous ulceration. In an analysis of 216 clinical specimens of gastric ulcer and gastric cancer, he found cancer arising in chronic ulcer fourteen times.

M. M. Canavan.

Embryoma of the Testis: Sudden Death from Thrombosis of Pulmonary Veins. A. E. Webb-Johnson, Brit. M. J. **2**:1048, 1925.

An Army officer, aged 31, was admitted to a base hospital on account of a condition diagnosed as "lumbago." He said that he was comfortable in bed but suffered pain on movement. This he had noted for a little more than a month. He fell to the floor in a moribund state the day after entrance to the hospital while chatting with another patient, and died in a few minutes. Thrombi were found in the pulmonary veins, and masses in the posterior mediastinum and in the right lumbar region, and a tumor in one testicle, which proved to be an embryoma.

M. M. Canavan.

Endometriomata. S. Herd, J. Obst. & Gynec. Brit. Emp. **32**:649, 1925.

Two groups of cases were studied, the first comprising twenty-five cases of true aberrant endometrial tissue, the second three nonendometrial lesions. Herd uses the term "endometrioma" in preference to "adenoma," "adenomyoma" or "endometriosis." The development of chocolate or tarry cysts occurs in three stages. In the first the cyst lining has columnar epithelium, occasionally ciliated, and the nuclei for the most part are centrally located; the walls of the cyst may contain endometrial glands and stroma. In the next stage signs of atrophy are noticed. In the last there is complete inactivity, and typical chocolate cyst material is seen. It is not unusual to find endometrial tissue in abnormal situations in and about the pelvis. Such tissue corresponds with the uterine endometrium in all the latter's physiologic phases, and shows the reactions of menstruation, decidua formation and the menopause. The most frequent situations for endometriomas are the uterus and ovary. They may occur rarely in the round and uterosacral ligaments. The ovaries in Herd's series presented adhesions, which were more marked as the invasion became more intensive, and in the more extensive growths endometrial tissue could be found in the adhesions of the ligaments of the ovary, of the peritoneum of the pouch of Douglas and of the adjacent bowel. The clinical factors associated with this condition are usually that of history of sterility with symptoms of acute pain in the lower part of the abdomen and dysmenorrhea occurring in women at the ages of 40 to 50. According to the author, endometrial invasion of the ovary may occur by direct implantation, by extension along the ovarian ligament, by metaplasia of crypts of the ovarian capsular epithelium and by metaplasia of tubal fimbriae which have invaded the ovary.

A. J. Kobak.

Accidental Transmission of a Malignant Tumor in Man. P. Lecène and A. Lacassagne, Ann. anat. path. et anat. normale méd.-chir. **3**:97, 1926.

Lecène and Lacassagne report a case in which a neoplasm has been apparently transmitted from one human being to another. A medical student, aged 21, while puncturing a lymphatic pouch formed beneath the scar of an amputated breast for cancer, punctured his hand to the bone through the palm. The wound

was cauterized about forty-five minutes after the accident. Two years later he began to feel a diffuse pain in his hand, in the area which had been wounded previously; this was soon followed by an irregular, hard swelling. One month later, a few enlarged lymph nodes appeared in the axilla, which were removed and diagnosed as "chronic inflammation." The swelling of the hand persisted, and in one area it became ulcerated. There was considerable difficulty in moving the finger. The hard nodules from the hand were then removed, and histologic examination of the removed tissue showed that it was unmistakably malignant. Following operation the growth of the tumor seemed to be accelerated, and in a few weeks four nodules appeared under the skin of the forearm, and microscopic examination showed them to be neoplastic, similar to the previously removed growth. A disarticulization of the shoulder was then performed. One year following the operation, the patient was in good health.

The outstanding feature of the case is: The tumor of the breast removed at operation was an atypical medullary epithelioma, while the new growth which developed in the student's hand following the accidental trauma was a spindle cell sarcoma. The authors propose several hypotheses to explain the change in the type of tumor: (1) Such a transformation could be effected under the influence of adaptation to the new host, a phenomenon observed by Ehrlich and Apolant in the transmission of certain tumors in mice; (2) the tumor in the student, was in reality epithelial in nature, but, owing to the new terrain, it had become extremely atypical; this hypothesis is strengthened by the fact that the growth was transmitted by way of the lymphatics, which is in favor of its being of epithelial rather than of connective tissue origin; (3) the transmission of the cancer was effected either by the inoculation of a filtrable virus analogous to that described by Gye, or by an "infecting principle" advocated by Carrel. The possibility of the tumor in the student being a sarcoma which had developed independently under the single influence of trauma, due to the puncture by the needle, is mentioned by the authors, but is rejected as being inadmissible. The article is accompanied by eight plates illustrating the tumor of the breast as well as that of the student's hand.

B. M. Fried.

Statistical and Critical Considerations of the Relation of Trauma to Tumors. G. Villata, Policlinico **32**:451, 1925.

Of 762 malignant tumors, seventeen (2.23 per cent) developed in close connection with trauma. The clinical histories of these cases are given in brief, and the conclusion is drawn that trauma plays a certain rôle in the development of malignant tumors, but just how is not known.

Serologic Test for Cancer. N. Capizzano, Bol. Soc. obst. y ginec. **4**:597.

In twenty-five women without any indications of cancer, the fluid remained yellow when 5 drops of a 0.03 per cent solution of neutral red were added to 2 cc. of blood serum. In twenty-four cases of carcinoma of the cervix or of the body of the uterus the tint of the fluid was pink in 70 per cent.

Precancerous and Definitely Cancerous Lesions and Their Relation to Cholesterin. A. H. Roffo, Bol. d. Inst. med. exper. **2**:11, 1926.

A large amount of cholesterin was found in precancerous lesions of the skin as well as in fully developed cancer. This accumulation might be the

result of the metabolic changes due to the neoplasm, or rather, in view of its presence in the early lesions, the associated hypercholesterinemia and the influence of cholesterin in the alimentary tract on the development of neoplasms, it is probably one of the precursory conditions, and is certainly involved with the enhanced nutritional function of tissue growths as known in neoplasms and pregnancies.

E. B. Perry.

Spindle Cell Sarcoma of the Tongue. A. H. Roffo, Bol. d. Inst. med. exper. **2**:32, 1926.

A spindle cell sarcoma of the tongue is described as rare. Its development at the site of lodgment of a fishbone suggests that irritation was of etiologic influence in this as in the tumor reported by Serafini, which followed injury of the tongue by a splinter.

E. B. Perry.

Toxic Action of Tumors. A. H. Roffo and R. Lopez Ramirez, Bol. d. Inst. med. exper. **2**:52, 1926.

The toxic effects of fresh extracts of sarcoma and carcinoma were not considered specific, because similar effects were obtained with extracts from normal tissues; all produced lowered blood pressure. The necrosis seemed to be an important factor in the toxicity, for young tumors without a zone of necrosis were less toxic. Both sarcoma and carcinoma extracts could produce death, but more toxic symptoms were induced by the carcinoma products.

E. B. Perry.

Melanin Separation After Roentgen-Ray Treatment of Melanosarcoma. J. Borak and F. Driak, Klin. Wchnschr. **5**:411, 1926.

Extensive irradiation of melanosarcoma nodules produces a separation of melanin and melanogen.

Arthur Locke.

On the Influence of Glucose Administration on the Growth of Tar Carcinomas. P. Rondoni, Klin. Wchnschr. **5**:465, 1926.

Glucose injections favor the growth of tar carcinomas in rabbits.

Arthur Locke.

The Lactic Acid Content of the Blood in Carcinoma. H. Schumacher, Klin. Wchnschr. **5**:497, 1926.

Injury to the liver of a patient who has carcinoma produces an increase in the blood lactic acid content.

Arthur Locke.

Hemagglutinins in Cancer. F. Schiff, Med. Klin. **22**:455, 1926.

Schiff attributes Weitzner's results, showing a peculiar relation between cancer and certain blood groups, to error from pseudoagglutination which is frequent in the blood from cancer patients. Cancer patients show about the same percentages of blood groups as healthy people of the same locality.

SIGNIFICANCE OF THE ALIMENTARY LEUKOPENIA OF WIDAL FOR CANCER DIAGNOSIS. K. RAUSCHE, München. med. Wchnschr. **73**:441, 1926.

Carcinoma is accompanied by alimentary leukopenia (Widal) in 80 per cent of the persons examined. The positive leuko-Widal test is not, however, specific for carcinoma, and may be used for the diagnosis of cancer only together with a careful consideration of the clinical observations. A negative leuko-Widal reaction indicates the absence of carcinoma more strongly than a positive one indicates its presence.

ARTHUR LOCKE.

EXPERIMENTAL UTERINE CANCROID. TEUTSCHLAENDER, Ztschr. f. Krebsforsch. **23**:161, 1926.

Intravaginal injections of tar into a rat were followed by cancroid of the uterus.

TUMOR AND TRAUMA. F. SAUERBRUCH, Nederl. Tijdschr. v. Geneesk. **69**, suppl. 11, 1925.

Trauma alone is not the cause of tumor growth, but it may be the occasion for the development of tumor on a predisposed basis. These relations are illustrated by keloid, xanthoma and ostitis fibrosa. It must be acknowledged that certain observations indicate the possibility of a malignant tumor arising in consequence of a single trauma; this, however, is exceptional.

GANGLIONEUROMA IN CERVICAL SYMPATHETIC. F. HARBITZ, Norsk Mag. f. Laegevidensk. **87**:371, 1926.

The tumor, which was of a fibrous structure with numerous ganglion cells, was removed from a woman, aged 22, who had noticed it since her second year.

TUMORS IN FISH. K. TAKAHASHI, Gann. **19**:5, 1926.

Takahashi has collected 140 tumors in fishes, including practically all kinds of growths except myomas. Only one instance of a neuroma was found. Tumors containing guanin crystals — his "guanophoromas" — have never been found in warm-blooded animals. Sagawa describes a case of multiple fibromas on the skin of a gold fish, epitheliomas, and osteomas in other fishes. None of the tumors seemed to be of parasitic origin.

Medicolegal Pathology

ANOMALIES OF DEVELOPMENT IN THOSE WHO COMMIT SUICIDE. A. J. KRJUKOW, Deutsche Ztschr. f. d. ges. gerichtl. Med. **7**:38, 1926.

From an experience in postmortem examinations especially for medicolegal purposes extending over twenty-five years, this address at the convention for legal medicine in Moscow in March, 1924, emphasizes the usefulness of maceration to bring out irregularities of surfaces and sutures so common in the skulls of those who commit suicide. The sutures normally closed by fibrous union are bony altogether or in spots, and such firm union occurring prematurely is followed by greater sharpness of the ridges and the angles, ridges which on the inner surface of the cranial bones form boundaries for depressions also are accentuated in such skulls. Frequently there are asymmetric spots

of translucent thinness without diploe; less commonly, great thickness, from 10 to 15 mm., is encountered, such heavy cranial bones being much smoother inside. These anomalies have long been noted in the skulls of the insane and Krjukow merely claims that they are more frequently encountered in skulls of those who commit suicide than otherwise. He also mentions as common in cases of suicide lessened circumference of the aorta (from 4.5 to 6 cm. at the root); increased weight of the brain (from 1,400 to 1,600 and exceptionally 1,720 to 1,760 Gm.), and the lymphatic constitution with persistence and overgrowth of the lymphoid tissue of the thymus, as Bartels reported in 1908.

E. R. Le Count.

Medicolegal Experience with, and Experimental Investigations of, Revolver Wounds. F. Kipper, Deutsche Ztschr. f. d. ges. gerichtl. Med. **7**:60, 1926.

The affianced of a man shot in a restaurant fight claimed at the time when he was shot that she was embracing him from behind and therefore was positive he was not among those attacking the accused. This Kipper denied because the wounds were through the soft parts of the thorax, through and through, and made by a bullet of large caliber, 7.65 mm., and he claimed that had she been placed as alleged, she too would have been wounded. The results of experiments (*Deutsche Ztschr. f. d. ges. gerichtl. Med.* **5**:193, 1925) in shooting at dead bodies with revolvers made by various manufacturers and of two calibers, 6.35 and 7.65 mm., supported his opinion, for as a rule the larger bullets went through and the smaller lodged.

In a review of fifty-six bullet wounds found in his postmortem work (*Deutsche Ztschr. f. d. ges. gerichtl. Med.* **5**:553, 1925), Berg objected to Kipper's conclusions, stating that factors influencing resistance and deviation were not the same in dead as in living bodies, for he had found that twenty-four of the fifty-six bullets had lodged and only two were of caliber less than 7.65 mm.

Challenged to do so by Berg, Kipper now reviews the conditions directly related to the issue between them as encountered in the postmortem work in Berlin. His summary deals with forty-three fatal wounds due to bullets of 6.35 mm. caliber, forty-one to those of 7.65 mm. and thirty-three from bullets with a caliber of 9 mm. His first contention that larger bullets generally go on through and out of the body is apparently supported. Only seven of the forty-one with a caliber of 9 mm. lodged, and fourteen of the forty-one with 7.65 mm. caliber; whereas only six of the 6.35 mm. bullets, forty-three in all, passed through the bodies.

There are many interesting references in these discussions by Berg and Kipper to influences which may greatly modify the features of the wounds made by bullets, and among these perhaps the nature and quality of the powder is as important as any and its deterioration in the cartridges from various causes such as chemical changes due to the various metals now used as coverings for the lead.

E. R. Le Count.

Fatal Poisoning with Amidopyrine. Torben Geill, Deutsche Ztschr. f. d. ges. gerichtl. Med. **7**:344, 1926.

In connection with a medicolegal inquiry, the postmortem examination made by Haberda having failed to find any disease to explain death, Geill was led to summarize the pharmacologic and toxicologic actions of amidopyrine,

sedative, anodyne and hypnotic. It was demonstrated that this drug was the cause for death as enough was recovered to correspond to 3 Gm. in 4 Kg. of material one fourth of which was quantitatively examined. It was estimated that many times this amount had been taken by the young woman who apparently had been using the drug for headaches. The stomach washings during life were not preserved.

Geill states that this is the first instance of death from this drug. He mentions a case of poisoning reported by Rotky in Prague which, however, was not fatal. The recovery was a matter of weeks during which there were intermittent attacks of fever, the more immediate symptoms being subnormal temperature, a pulse too rapid to count, general trembling with chillness, and mental anxiety. On the second day after the poisoning great tenesmus and frequent urination of a dark red urine with which ferric chloride gave a beautiful red color were observed; on the third day a measles-like rash appeared on the neck and shoulders and in the buccal and pharyngeal mucosa.

In Geill's case of fatal poisoning, death took place abruptly. The material washed from the stomach was foamy like soap-suds and at the necropsy a similar foam was present in the air passages. Some of the foamy material from the stomach developed an odor like raspberries when it had been kept for a day or so in a stoppered bottle.

E. R. Le Count.

Air Embolism from a Superficial Wound of the Neck. K. Böhmer, Deutsche Ztschr. f. d. ges. gerichtl. Med. **7**:350, 1926.

A wounded man was found dead about seventy steps from where, after a drinking bout, a brawl occurred on the street. Later the assailant said he had noticed that blood about the wound was frothy with many fine bubbles. The left external jugular vein was found severed close to a branch which formed an anastomosis with the internal jugular. The pericardial sac was filled with water at necropsy and in it the heart floated, as it contained considerable fine froth in the right ventricle. Then the old difficulty arose, namely, the question whether the foam in the heart was due to gas formed after death, and quite properly, since necropsy was performed eighty-four hours after death. Böhmer now measured the amount of gas in the hearts of ten persons dying from various causes but with no question of air embolism. These details are given in a table with records of the temperature, barometric conditions, bacteriologic examinations of the blood, causes of death, time after death that the examinations were made, etc. This rather elaborate control investigation amply justified his conclusion that death in the particular case was due to air embolism. Of special interest is the entire absence of gas in the heart sixty-five hours after death in the frozen body of a woman who died from corrosive sublimate poisoning.

E. R. Le Count.

Air Embolism in Criminal Abortion. J. P. L. Hulst, Nederl. Tijdschr. v. Geneesk. **1**:759, 1926.

In one of the two cases described death occurred instantaneously after the first symptoms of air embolism, eighteen hours after the intra-uterine injection of a warm liquid. Air was found between the uterine wall and the (twenty-three weeks) ovum, but no air was found in the fetal membranes. In both cases the right side of the heart was ballooned out with air and air was in both coronary arteries and veins. Both necropsies were made about twelve hours

after death and Hulst admitted the possibility of a gas bacillus infection in the first case as frequent intra-uterine injections had been made. In the second case the broken cannula tip pierced the right vaginal wall and entered an artery and death was instantaneous.

J. De Vries.

Technical

An Adaptation of the Kolmer Wassermann Technique to Tuberculosis Complement Fixation. J. S. Woolley and F. G. Petrik, Am. Rev. Tuberc. **13**:243, 1926.

A modified Kolmer technic is described for complement fixation in tuberculosis. Icebox incubation is substituted by waterbath incubation. Glycerine extract of dried tubercle bacilli (a modification of Petroff's antigen) is used as antigen. Of 180 patients with clinical tuberculosis, 83 per cent reacted positively (only 3 plus and 4 plus reactions considered as positive; the percentage is about 72). Cross fixation with serums of "certain syphilitics" were observed, but only a very small percentage of nonspecific reactions.

Max Pinner.

Eliminating a Source of Error in the Laboratory Diagnosis of Rabies. Earle K. Borman, Am. J. Pub. Health **14**:467, 1926.

In order to avoid the potential source of error due to the fixation of red blood cells in or on brain tissue the following method is recommended:

The brain should be dissected out and impressions and smears made from Ammon's horn, the cerebellum and the cerebral cortex in the usual manner. The layer of tissue on each slide should be made as thin as possible, for a thick layer is more easily washed or rubbed away with subsequent treatment. The slides should be placed in the following solution: chemically pure methyl alcohol, 98 cc., and glacial acetic acid, 2 cc. The slides should be allowed to stand in this solution for three minutes and then dried quickly over a flame, care being taken to avoid intense heating. The slides should then be transferred to a 10 per cent aqueous solution of potassium carbonate and allowed to stand thus for five minutes. After this they should be washed in a gentle stream of tap water and dried by blotting gently with smooth absorbent paper. Care must be taken not to wash or rub away any of the tissue adhering to the slides. The slides should next be flooded with the following dye mixture: methylene blue (saturated aqueous solution) 3 drops; basic fuchsin (saturated alcoholic solution) 2 drops, and tap water, 20 cc. The slides should be warmed by being passed once through a flame. They should be allowed to stain for not more than one minute. The staining time will depend on the purity and solubility of the dyes used. The slides should be washed in a stream of tap water, dried and examined for Negri bodies. Any stain which will demonstrate the presence of Negri bodies may be used. The foregoing stain, which is in use in many laboratories, has, however, given the most consistent results with this method. This stain should be reddish-blue, the red dye should not dominate the blue. It must be kept at icebox temperature when not in use. It should never be used after standing for more than twenty-four hours, as it deteriorates rapidly.

A slide properly prepared by this method should show the large nerve cells with reddish-blue cytoplasm and deep blue nuclei in a matrix of brilliant red.

Negri bodies, if present, will then be a characteristic strawberry red with typical granular structure. Unstained, vacuole-like areas will be perceived where red blood cells were located.

HEPARIN-PLASMA AS STOCK-PLASMA FOR TISSUE CULTURES. E. C. CRACIUN, Bull. Johns Hopkins Hosp. **38**:327, 1926.

Heparin-plasma meets all requirements for tissue culture. It is specially advantageous in experiments requiring longer time and many series of cultures. Blood is drawn into a syringe which contains a 1:1,000 or 2:1,000 solution of heparin, and the ratio of heparin to blood should be 1:10,000:20,000. The heparinated blood is poured into a cold tube and placed on ice for from three to five minutes, and then centrifugalized, the clear plasma being transferred to 1 or 2 cc. ampules which are sealed and kept in a cool place in the dark. This plasma is ready for use at any time and may be kept for at least seven months.

THE MAGNITUDE OF THE ERROR DUE TO AMMONIA AND ITS SALTS IN THE VAN SLYKE AMINO NITROGEN PROCEDURE AS COMMONLY APPLIED IN STUDIES OF BACTERIAL METABOLISM. L. B. PARSONS and W. S. STURGES, J. Bact. **11**:153, 1926.

The presence of ammonia in the material examined may cause a serious error in the determination of amino nitrogen by the Van Slyke method. Accurate determinations may be obtained after the ammonia has been removed.

ARTHUR LOCKE.

A STUDY OF THE MOLYBDIC OXIDE COLORIMETRIC METHOD FOR THE ESTIMATION OF THE PHOSPHORUS COMPOUNDS OF THE BLOOD. J. H. ROE, O. J. IRISH and J. I. BOYD, J. Biol. Chem. **67**:579, 1926.

A COLORIMETRIC METHOD FOR THE ESTIMATION OF BLOOD CALCIUM. J. H. ROE and B. S. KAHN, Ibid. **67**:585, 1926.

"A colorimetric method for estimating blood calcium has been developed which is based on the precipitation of calcium as phosphate, and the determination of the latter by the molybdic oxide colorimetric procedure. The method is accurate and is a successful micro procedure, being adaptable to much smaller quantities of serum than other methods in use at the present time."

AUTHORS' SUMMARY.

HETEROPHIL ANTIGEN-ANTIBODY REACTIONS. IN RELATION TO THE SERUM DIAGNOSIS OF SYPHILIS BY PRECIPITATION. SANFORD BURTON HOOKER, J. Immunol. **11**:403, 1926.

The observations by Taniguchi, Schmidt and others that alcoholic extract of guinea-pig heart sometimes may cause a false positive test when used as antigen in the Wassermann reaction is confirmed in this report. This false positive reaction can be due to the presence in certain human serums of lysin for sheep corpuscles; this lysin is a so-called heterophil antibody because it unites not only with sheep corpuscles but also with substances (heterophil antigens) in the organ cells of guinea-pigs and certain other animals.

Obviously, human serum containing this lysin may react in fixation or precipitation with extracts of guinea-pig or other heterophil tissue. Fortunately, beef heart is not heterophil in this sense. Laboratories that use extracts of guinea-pig or horse heart as antigens in the Wassermann test should not fail to take into account that positive reactions may be produced through a nonsyphilitic mechanism.

URINARY PRESERVATIVES INCLUDING HEXAMETHYLENAMINE. J. A. BEHRE and W. MUHLBERG, J. Lab. & Clin. Med. **11**:785, 1926.

A preservative which seems to fulfil the requirements for practical urinary analysis consists of a mixture of hexamethylenetetramine and salicylic acid in the ratio of three parts to two. Fifty milligrams of the mixture are used for the preservation of every 10 cc. of urine.

S. A. LEVINSON.

THE CLINICAL VALUE OF THE ERYTHROCYTE SEDIMENTATION REACTION IN SURGERY. E. RUBIN, Surg. Gynec. Obst. **42**:663, 1926.

Since the work of Fahraeus in 1918 over 300 reports have appeared on the so-called erythrocyte sedimentation reaction. The consensus of opinion in these is that the test is a valuable adjunct in following the course of a disease, being useful as an indicator of the degree of toxicity of a pathologic process and of the reaction of the patient. The sedimentation test utilizes the speed with which red blood cells settle in a citrated column of blood, which is determined either by observing the distance which the cells have settled in a given period of time (Westergren method) or by noting the time it takes for the top layer of cells to reach a certain distance in the container (Litzenmeier method). The author using the method of Moniss, which gives the sedimentation values in volume per cent of the entire columns of blood, studied a large number of acute and chronic surgical conditions. He found that the graver lesions are accompanied by more accelerated sedimentation reactions. Increases in sedimentation followed surgical operations and, with the improvement of the patient, diminished gradually. Extrasurgical complications such as syphilis or tuberculosis tended to maintain high readings in spite of the improvement or even cure of the surgical condition.

M. L. PARKER.

A SIMPLE TEST OF DIAGNOSTIC VALUE IN GENERAL PARESIS. J. S. HARRIS, Brit. M. J. **2**:136, 1926.

Periodically less time consuming tests than the Wassermann and the routine colloidal gold test and cell counts are sought to aid those interested in the diagnosis of syphilis of the nervous system. This article is based on lumbar punctures of 180 patients with mental diseases the fluid being tested as follows: 1 cc. of cerebrospinal fluid is added to 0.3 cc. of acetic anhydride; the mixture is shaken well and 0.8 cc. of concentrated sulphuric acid added drop by drop. Held against a white background a lilac tint indicates a positive reaction (this may appear instantly and last five minutes or disappear sooner), while brown-yellow or red-yellow is negative. The reaction is thought to depend on the presence of cholesterol in the cerebrospinal fluid. They find this present in 97 per cent of the cases.

M. M. CANAVAN.

STAINING OF INTERCELLULAR SUBSTANCE. J. M. PETRIE, M. J. Australia **1**:163, 1926.

It has been demonstrated by Petrie that the intercellular material forming the semifluid "ground substance" in certain endothelial tissues can be stained and made visible. This is due to the presence of a potassium compound in the substance. Fresh tissue is laid on a slide and treated with cobalt. After a certain time the slide is washed with ice-cold water till the excess of reagent is completely removed. If the slide is now examined under the microscope, the intercellular substance is seen to be formed of yellow precipitate, which is the triple salt of cobalt sodium potassium nitrite; when the preparation is subsequently treated with ammonium sulphide, this yellow compound is changed to black cobalt sulphide, which is permanent.

NEED OF CAREFUL TECHNIC IN BLOOD GROUP TESTS. P. BADINO, Policlinico **33**:433, 1926.

Badino found panagglutinins in the plasma (obtained by addition of anticoagulants) and to a less degree in the serum which separated at the temperature of 16 or 37 C. The latter specimens agglutinated every blood, including their own, sometimes even at 16 C. He concludes that careful work — especially when the test cannot be made under exact thermal conditions — requires the use of test serums which separated from blood kept in the icebox for two hours. The panagglutinins are absorbed by the coagulum in this case.

THE PREPARATION AND IMBEDDING OF COMPLETE SECTIONS THROUGH THE THORAX. E. MILLER, Beitr. z. klin. d. Tuberk. **63**:360, 1926.

A method is described for preparing permanent sections through the whole thorax, preserving the organs in their natural relation.

MAX PINNER.

PRACTICAL HINTS FOR THE PREPARATION OF PATHOLOGIC AND OTHER MUSEUM SPECIMENS. W. TALALAEFF, Centralbl. f. allg. Pathol. u. path. Anat. **37**:196, 1926.

Detailed instructions are given for the preparation of museum containers consisting of front and back glass plates fastened to framelike wooden strips. Specimens are mounted in this chamber in an agar-mixture. Cheapness, durability, permanency and elimination of optical distortion have made this method preferable to preservation in liquids in Russia.

GEORGE RUKSTINAT.

REMARKS ON THE RABL METHOD FOR THE HISTOLOGIC DETERMINATION OF CALCIUM. E. FREUDENBERG, Klin. Wchnschr. **5**:64, 1926.

It is impossible to distinguish between soluble and precipitated calcium in tissue sections by the method of Rabl.

ARTHUR LOCKE.

THE TECHNIC OF MY THIRD SYPHILIS-FLOCCULATION REACTION. D. E. MEINICKE, München. med. Wchnschr. **73**:691, 1926.

An addition of from 0.3 to 0.5 per cent of benzoic acid to the original Meinicke extract (an alcoholic extract of ether-extracted horse heart) considerably increases its reactivity without impairing its capacity to give a specific floccula-

tion reaction with syphilitic serum. The principal modifications of the original method are based on a study of the effect of temperature on the production of suitable aqueous dispersions of the extract and on the character of the final flocculation. The technic of the new method is given in detail.

ARTHUR LOCKE.

BLOOD PLATELET INDEX IN PERNICIOUS ANEMIA. E. ALLARD, Zentralbl. f. inn. Med. **47**:258, 1926.

Allard figures this index by dividing by 50 the number of platelets per thousand erythrocytes. For instance, in normal blood (250,000 platelets and 5,000,000 erythrocytes per cubic millimeter) there are fifty platelets per thousand erythrocytes — the index is 1. In pernicious anemia, the index is usually low (0.2 and less). A low index is an unfavorable sign. It announces an exacerbation even if the red count is comparatively high. A high index with low erythrocyte count frequently precedes a remission. No significant remissions can be expected with less than 100,000 platelets per cubic millimeter.

KAMIL SCHULHOF.

A SIMPLE METHOD FOR DIFFERENTIATION OF MYELOID AND LYMPHOID LEUKOCYTES OF HUMAN BLOOD. A NEW PEROXIDASE REACTION (COPPER METHOD). AKIRA SATO and SOTOKICHI SEKIYA, Tohoku J. Exper. Med. **7**:111, 1926. SEE ALSO: PEROXIDASE REACTION IN ENCEPHALITIS. A NEW DIAGNOSTIC AND PROGNOSTIC METHOD. AKIRA SATO and SOTOKICHI SEKIYA, Am. J. Dis. Child. **29**:301, 1925.

A new peroxidase stain is described using: solution A, copper sulphate 0.5 per cent; solution B, 0.2 Gm. of benzidine (P-diamino-diphenyl) rubbed with a few drops of water in a mortar, then 200 cc. of water added at room temperature and filtered, and to the filtrate 4 drops of a 3 per cent solution of hydrogen peroxide added; solution C, the counter stain, of neutral red, carbolfuchsin (1 part in 5) or safranin, aqueous solution 1 per cent, which is the best. Apply solution A to a fresh blood smear. Pour off most of it and apply solution B for two minutes and wash thoroughly with water. For counter staining do not pour off the peroxidase stain, but add solution C at once, let stand two minutes and wash, or apply 1 drop of safranin, aqueous solution 0.05 per cent, to a cover slip, put it on the peroxidase stained smear and examine at once.

The copper sulphate, both of whose ions aid the blue color of the myeloid granules which contrasts clearly with the light brown erythrocytes and the pale cytoplasm of the lymphocytes, also makes previous fixation unnecessary. It is claimed that the myeloid cells in blood from epidemic encephalitis are negative with this peroxidase stain although still positive with the Winkler-Schulze oxidase stain. Since this negative change does not occur in influenzal, tuberculous or acute meningitis or epidemic poliomyelitis the conclusion is that this test can be used in the differential diagnosis and prognosis of acute epidemic encephalitis, the length of staining time necessary to return to a positive reaction being in direct proportion to the gravity of the disease.

ETHEL B. PERRY.

Society Transactions

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Regular Meeting, May 13, 1926

EUGENE L. OPIE, *Presiding*

SARCOMA OF UTERUS. HAROLD G. PALMER.

It is an established fact that when compared with carcinoma the occurrence of sarcoma of the uterus is relatively rare. Two distinct anatomic areas may be involved, the muscularis and the mucosa. In the wall the neoplasm may be submucous, intramural or subserous. In the endometrium it may be polypoid or diffuse. Wherever located it may show wide variation in size and in clinical manifestation before it comes under surgical observation. The tumor may be definitely encapsulated or grow wild. In the latter event, metastases are usually early and extensive and the prognosis correspondingly more hopeless.

The lungs and liver are usually the organs first invaded by metastatic nodules. Thrombosis of regional veins by tumor cells may occur without metastases to distant organs. Round cell and giant cell tumors are considered most malignant. Genetically, sarcoma wherever located is considered as a mesoblastic tumor. At present there is considerable academic discussion regarding the exact origin of uterine sarcomas. Neoplasms arising in the endometrium are conceded to be of stromatic origin; on the other hand, mural tumors are considered of myogenic origin.

Cell metaplasia, a reversion to embryonal cell type, I believe, is a more frequent occurrence than generally recorded.

Two tumors showing evidence of such metaplasia are presented.

CASE 1.—*Sarcoma of Uterus with Metastatic Implants in Uterine Wall.*—A white woman, aged 34, a nullipara, had a normal menstrual history with the last period two weeks before operation. The preoperative diagnosis was ovarian cyst and uterine myoma. At operation the uterus presented the typical picture of a four months' pregnancy, accentuated when a subsequent incision of the specimen released what was apparently amniotic fluid.

The essential points of the pathologic examination were: The gross specimen was 8 by 10 by 15 cm., consisting of a uterus with appendages, and a large encapsulated intra-uterine tumor, with two metastatic nodules in the uterine wall. The main tumor on section was lobulated and resembled the cotyledons of placenta. The metastatic tumor was soft, smooth and homogenous. Microscopically the neoplasms were identical and consisted of round and spindle cells with incidental islands of myomatous tissue containing mature blood vessels. The tumors had a generous vascular supply through immature channels. The right broad ligament contained a unilocular cyst 8 by 13 cm. filled with clear fluid.

CASE 2.—*"Simultaneous Occurrence of Adenocarcinoma and Sarcoma in the Same Uterus."* (Reported by Jones and Palmer: *Am. J. Obst.* **63**:449 [March] 1911).—The case was presented with the original photographs for review. The patient is living and well, sixteen years after operation.

SARCOMATOUS CHANGE OF FIBROID OF UTERUS. FRED HARTMANN.

A white woman, aged 62, was admitted to the medical service of the Lankenau Hospital, April 16, 1926, in a moribund condition.

The patient had been well until nine weeks before admission, when she noticed shortness of breath and a beginning swelling of the feet and ankles. Shortness of breath became more marked, and the swelling spread to her legs and thighs. At the same time the abdomen became markedly distended and enlarged. The skin was marble white. The patient was sitting propped up in bed, showing marked dyspnea. The chest showed marked limitation of motion on respiration, especially on the left side. This side gave all signs of a massive pleural effusion. There was a moderate amount of fluid at the base of the right lung. The heart sounds were distant and weak. A faint mitral systolic murmur was heard at the apex. The abdomen was markedly distended with fluid. No masses could be palpated with the patient in the sitting position. The extremities showed marked edema. The patient grew worse rapidly, and died of pulmonary edema within eighteen hours after admission. A clinical diagnosis was made of chronic myocarditis with marked decompensation.

Necropsy revealed the abdomen to be distended markedly with bloody fluid, the amount estimated at 10,000 cc. Springing from the pelvis was a large fleshy, red and bluish mass extending up into the true abdomen, and infiltrating the mesentery of the small bowel. The total size of the mass was about that of a fetal head. The mass was friable and vascular. It was found to originate from a large subserous fibroid of the uterus measuring 12 cm. in diameter. This fibroid showed marked degeneration with necrosis and calcification. The entire peritoneal cavity and all of the loops of the bowel were studded with small reddish, fleshy, tumor-like growths.

The spleen showed two small metastatic nodules (evidence of blood metastasis). The liver showed no evidences of metastasis. The kidneys were the seat of cloudy swelling and arteriosclerotic changes. The gallbladder was filled with numerous yellowish-black calculi. The left pleural cavity contained approximately 1,500 cc. of bloody fluid. Practically the entire pleural surface was studded over with secondary growths similar to those found in the peritoneal cavity. The right pleural cavity presented the same condition to a less marked degree. Both lungs showed marked infiltration with the growth. The heart weighed 320 Gm. and showed moderate sclerosis and myocardial degeneration. In the right ventricular wall was a metastatic nodule measuring 1 cm. in diameter. This projected into the right ventricle, pushing the endocardium ahead of it. The microscopic diagnosis was large spindle cell sarcoma.

The case was of interest: first, as a mistake was made in diagnosis that could only have been proved by necropsy; secondly, because of the rarity of metastases to the heart and to the spleen without any involvement of the liver, and thirdly, because of the dangers associated with so-called benign fibroids of the uterus. They are apt to become malignant, to cause marked bleeding with anemia and to give symptoms of focal infection. This last has been seen when cases of mild carditis or neuritis have cleared up after the removal of fibroids.

SPIROCHETAL PULMONARY GANGRENE. JOHN T. BAUER. (From the Ayer Clinical Laboratory, Pennsylvania Hospital, Philadelphia.)

The resemblance of this disease to other pulmonary diseases for which it has been mistaken, the increasing frequency of its recognition and the apparently satsfactory therapeutic response to arsphenamine justify the presentation of this case.

Case Report.—An American laborer, aged 43, was admitted to the Pennsylvania Hospital, Jan. 28, 1926, with the complaint of pain in the lower left side of the chest. He had been in the hospital two years previously suffering from pneumonia. The present onset was acute, starting ten days before admission with a cold and paroxysmal coughing, which was later productive of yellow mucopurulent sputum. The pain in the right side of the chest subsided to a constant dull ache radiating across the abdomen and lumbar region. On physical examination he appeared to be well developed, obviously sick and slightly cyanotic. His gums were retracted exposing the roots of foul and carious teeth. Physical signs suggested consolidation of the lower lobe of the left lung, and a clinical diagnosis of bronchopneumonia was made. About the twenty-second day of his disease, fluid was detected in the left pleural cavity and 750 cc. of thick yellow fluid was aspirated. This material had a rather fetid odor, not quite comparable to the foul smelling pus associated with abscess of the lung. Bacteriologic studies revealed the presence of many saprophytic bacilli and suggested the presence of a pulmonary abscess.

Thoracotomy was performed twenty-six days after the onset of the disease, followed by improvement for a few days; but his temperature which had returned to normal again rose and became hectic. He died sixteen days later, a month after admission. He had an average leukocytosis of 20,000, of which 85 per cent were polymorphonuclear neutrophils. The roentgenologic observations were extraordinary in representing both a loculated cavity and a pyopneumothorax on the left side.

The important results of necropsy were those associated with the thoracic contents. A large loculated abscess cavity containing fetid pus existed between the left lung and the diaphragm. It did not appear to drain into the major portion of the pleural cavity and was separated by dense adhesions from the thoracotomy opening. The left lung was partially atelectatic and a large multilocular cavity occupying the lower lobe had ruptured inferiorly producing the empyema. This was apparently the oldest lesion. Scattered throughout the remainder of the lung and more extensively throughout the right lung were many small punched out areas of necrosis, sharply separated from normal lung substance by a slightly necrotic membrane and a ring of hemorrhagic consolidation.

Examination of scrapings from the walls of the cavities with the dark-field microscope, several hours after removal, revealed the presence of many, irregularly sized, actively motile spirochetes, with large wide coils, moving intermittently and frequently bending at right angles. Direct smears of this material contained few pus cells, many fusiform bacilli, and spirochetes, in addition to other organisms.

A study of the walls of the necrotic cavities in microscopic sections revealed the absence of an inflammatory reaction about them.

With MacCallum's bacterial stain the spirochetes were demonstrated in the tissue in enormous numbers, occurring in distinct groups in the necrotic areas, whereas elsewhere they were relatively scarce. Many of the spirochetes were large, two and three times thicker than usual, and suggested longitudinal division. Irregular curves existed, but in general the organisms tended to curve much less than in directly stained smears and in the dark field preparation. No fusiform bacilli were seen. American investigators have identified this organism with the spirochete of Vincent.

This case seems to conform with the disease described by Pilot and Davis (Studies in Fusiform Bacilli and Spirochetes; Their Rôle in Pulmonary

Abscess, Gangrene and Bronchiectasis, *Arch. Int. Med.* **34**:313 [Sept.] 1924), Kline and Blankenhorn (Spirochetal Pulmonary Gangrene, *J. A. M. A.* **81**:719 [Sept. 1] 1923) and others as spirochetal pulmonary gangrene.

INDICAN—ITS PERIODICITY OF ELIMINATION. G. J. SAXON.

Indican is eliminated tidally, and a correct evaluation of the clinical worth of the test for indican in the urine must premise that the test has been performed by accurate quantitative methods on the twenty-four hour output, or that the simpler extraction colorometric methods have been employed on specimens collected every three or four hours over an arbitrarily chosen period, preferably not less than twenty-four hours.

As ordinarily done in hospitals and in private practice, a single specimen of urine is tested, or a composite of the night and morning urine is used, or a composite is chosen from the total twenty-four hour output. By the first and second plans one may miss the indican shower in from 15 to 85 per cent of the cases. By the third plan the total indican output may give only a feeble color reaction under conditions of high dilution that may exist.

Examination usually reveals the following as coexisting; coated tongue, fecal odor on the breath, vertigo or tinnitus, or both, headache, hyperchlorhydria or achylia gastrica, roentgen-ray diagnosis of seventy-two hour retention in the cecum and a laboratory report of no indican in the urine. The patient is instructed to procure six 1 ounce (30 cc.) bottles and to collect a specimen of urine at the time of each urination for a period of twenty-four hours. An indican test is made on one half of the contents of each bottle, using the bottle instead of a test tube for the reaction. Four of the specimens give a negative indican reaction; the remaining two give the most intensive reaction obtainable. The composite made up of the half content of each bottle gives a feeble indican reaction, dilution having interfered. It is not surprising that under such conditions indicanuria is regarded as an inaccurate criterion of intestinal stasis.

The followng deductions have been made from the results of more than 4,000 indican tests performed by the method of serial collection of specimens.

1. The indican reaction should be taken not on a single specimen but on a series of specimens collected serially during the entire twenty-four hours, at convenient intervals, so that in all six specimens may be used.

2. The indican reaction is a reliable guide to the degree of putrefactive cleavage in the intestines.

3. Under appropriate treatment the gradual disappearance of indican from the urine is commensurate with the disappearance of symptoms.

4. Under the most intensive treatment indican may not totally disappear, with a resulting "perfect score" for the patient, for from six months to two years.

5. The indican test properly carried out may greatly aid in the differential diagnosis of sinus headache from intestinal headaches, vertigo and tinnitus of intestinal origin from other forms, psychoses of intestinal origin from other forms, etc.

GASTRIC SECRETION FOLLOWING VARIOUS GASTRIC OPERATIONS. STANLEY P. REIMANN and L. SNELLBAKER.

This part of the report comprises the results of the estimation of acids before and after various gastric operations which were performed for peptic ulcers. Simple excision, posterior gastro-enterostomy with and without excision,

pylorectomy, the operations of Billroth number 1 and number 2, subtotal gastrectomy and the so-called Roux "Y" operation are included. No consistent differences from preoperative estimations were found except in the cases of subtotal resection in which the values for the acidity were all low. The methods consisted of examination of the contents of the stomach after fasting, and of fractional specimens following a standard meal of 250 cc. of water and 35 Gm. of bread. Results are given of two or more examinations made at intervals of from three to six months over a period of from one to five years following these various operations. The important clinical point is that relatively more of the patients who have had subtotal gastric resection performed are in better health than the others.

Book Reviews

A Classification of the Tumors of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis. By Percival Bailey and Harvey Cushing. From the Surgical Clinic and Laboratory of the Peter Bent Brigham Hospital and the Laboratory of Surgical Research of the Harvard Medical School. Cloth. Price, $5. Pp. 175, with 108 illustrations. Philadelphia: J. B. Lippincott Company, 1926.

On account of the painstaking description of the structure of gliomas, this book is of special interest to pathologists. The essential features of the book are stated clearly in a review in *The Journal of the American Medical Association*, July 24, 1926, page 268, and that review is reprinted here:

"Gliomas of the brain formed 42 per cent of a series of 1,000 intracranial tumors. Though such gliomas are usually regarded as early and inevitably fatal, the authors noted that many patients after incomplete extirpation of a cerebral glioma survived longer than expected, and this fact led them to make a thorough study of the structure and clinical history of 254 gliomas subjected to surgical treatment. Using the best modern methods for the microscopic study of glioma, the authors classify their gliomas according to structure and designate them in harmony with the terminology now used for cerebral histogenesis and histology. No less than thirteen classes of glioma are described, and to what extent this grouping will be accepted generally is of course something that will be determined in the future. From comparison of the structure with the clinical course, it emerges that gliomas composed of less differentiated cells are more active in growth than those made up of more differentiated cells. About half of the gliomas studied were comparatively benign except when inaccessible or so situated as to cause stasis of the arachnoid fluid. The survival of the patients varied from a few months to ten years or more, and the length of the survival period corresponded closely to the increasing differentiation of the glioma cells. The book is an important contribution to our knowledge of cerebral glioma, its life history, prognosis and treatment. It is a choice by-product of surgical work fully organized in the interest of investigation."

Post Mortem Appearances. By Joan M. Ross. Price $2.50. Pp. 216. Oxford Medical Publications. New York: Oxford University Press, 1925.

Dr. Ross describes the chief pathologic changes to be looked for in the bodies of persons dying from the common diseases and from poisoning. The accounts are necessarily brief, including only the typical changes and the gross appearances of the organs, but the essential facts are given in a clear manner. The book would be of value in making postmortem examinations, especially to one making occasional examinations, as the technic of performing the examination is described, as well as the lesions likely to be present in typical cases. There are tables of normal weights and measurements and a table of ossification of the bones useful for quick reference.